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Synthesis of Medium Ring Heterocycles by Directed C-C Bond Activation

Olivia Boyd

A thesis submitted to the University of Bristol in accordance with the requirements for award of the degree of Ph.D in the Faculty of Science

School of Chemistry, September 2020

(93994 words)

Author's Declaration

I declare that the work described in this dissertation was carried out between September 2016 and March 2020, under the supervision of Professor John F. Bower in the School of Chemistry, University of Bristol. The work was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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Abstract

In Chapter 1, a summary of transition-metal catalysed C–C bond cleavage of small ring systems that are pertinent to this thesis is presented. In Chapters 2 and 3, a modular Rh(I)-catalysed entry to various 7- and 8-membered *N*-heterocycles is outlined. Under an atmosphere of CO, aminocyclopropanes equipped with pendant nucleophiles undergo directed C–C bond activation to provide versatile rhodacyclopentanone intermediates. Subsequent intramolecular nucleophilic addition of an aryl or N-based nucleophile to the rhodacyclopentanone intermediate is followed by C–C or C–N bond formation to provide a range of sp^3-rich *N*-heterocycles. These studies demonstrate how the combination of cyclopropane strain release and the templating effect of catalytically generated metallacycles can be utilised to achieve challenging medium-sized ring closures.

Chapter 4 details a conceptual blueprint that enables direct and atom economical access to a selection of complex polyheterocycles. These processes capitalise upon the amphiphilic reactivity of rhodacyclopentanones for the construction of two new ring systems, the first of which is enabled by the intrinsic electrophilicity of rhodacyclopentanones, and the second by their latent nucleophilicity. Importantly, this reactivity mode is only unveiled by carbonylative C–C bond activation of a stable aminocyclopropane precursor. By using this approach, a diverse array of polycyclisations are achieved, including systems that involve powerful dearomatisations and medium ring formations.

In Chapter 5, studies are directed towards the total synthesis of (*rac*)-conolidine and related indole alkaloids. The newly developed 7-step synthetic route to (*rac*)-conolidine features a Rh(I)-catalysed carbonylative ring expansion of a cyclopropylamide to establish the 8-membered C-ring and a Ni(0)-catalysed enolate coupling to construct the azabicyclo[4.2.2]decane core.

Publications arising from this work:

1. Boyd, O.; Wang, G. W.; Sokolova, O. O.; Calow, A. D. J.; Bertrand, S. M.; Bower, J. F. *Angew. Chem. Int. Ed.* **2019**, *58*, 18844.

2. Wang, G.-W.; Boyd, O.; Young, T. A.; Bertrand, S. M.; Bower, J. F. *J. Am. Chem. Soc.* **2020**, *142*, 1740.

Acknowledgements

First of all, I would like to thank Professor John Bower for his much-valued support, advice and wise counsel over the past four years. His enthusiasm for chemistry has motivated me throughout my PhD and I am extremely grateful for my time in the Bower lab. I wish John all the best at the University of Liverpool, where he will no doubt continue to lead an excellent research group.

I would also like to thank Dr Sophie Bertrand, my industrial supervisor at GSK, for all her help throughout my PhD and, in particular, during my three month placement at GSK, Stevenage. Additionally, thank you to Dr Katherine Wheelhouse, Catherine Alder, Dr Phil Rushworth, Matt Gray and Maxime Rouah at GSK for their help and guidance in the lab.

I would like to thank the research staff at the University of Bristol for helping me throughout my studies. This list is by no means complete but thank you to Professor Craig Butts, Dr Paul Gates, Tom Leman, Sam Ferrins, Tony Rogers and Dr Hazel Sparks. I am especially grateful to Paul Lawrence for helping with NMR experiments.

Thank you to everyone in the Bower group for making my time in the lab such a fun place to work. Javi García Cárceles, it was great to work beside you in the main lab. Thank you also to Bedford group for welcoming us into their lab and the Wass group for the short time we spent with you.

A special thank you to Gangwei Wang for teaching me all about Rhodium and the lucky balloons. It was a pleasure to work with you and we made a great team.

Thank you also to CDT project students Hao Lan and Tim Aldhous for your hard work on some tricky projects.

My time in Bristol wouldn't have been half the fun it was without the following people, and for that I am eternally grateful. Phillippa Cooper, my lab mate from day one and great friend. Thanks for steering me through the wobbles and shared love of Anna Jones. Andrew Dalling, thank you for your friendship and love of aubergine parmigiana. Lauren O'Neil, thank you for the great lab music and summer BBQs. Sanita Tailor, thank you for your witty jokes. To the S.L.O.P. for cocktails and picky bits. To the boys: Tim Aldhous, Jamie Cadge, Steven Stanton, Ben Jones and James Wood for the many pub trips and memorable evenings. I will miss our Chicken dinners/drinks, but hopefully we will all get together soon.

Finally, I would like to thank my parents, brothers and sister, for their encouragement, love and support.

Abbreviations

ACP	alkylidenecyclopropane
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1’-bi-2-naphthol
CAN	ceric ammonium nitrate
cod	1,4-cyclooctadiene
CSA	camphor sulfonic acid
1,2-DCB	dichlorobenzene
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DG	directing group
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMP	Dess-Martin Periodinane
dppe	1,2-bis(diphenylphosphino)ethane
dppb	1,4-bis(diphenylphosphino)butane
dppp	1,3-bis(diphenylphosphino)propane
d.r.	diastereomeric ratio
DME	1,2-dimethoxyethane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.r.	enantiomeric ratio
HBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HOBt	hydroxybenzotriazole
IBX	2-iodoxybenzoic acid
KIE	kinetic isotope effect
LDA	lithium diisopropylamide

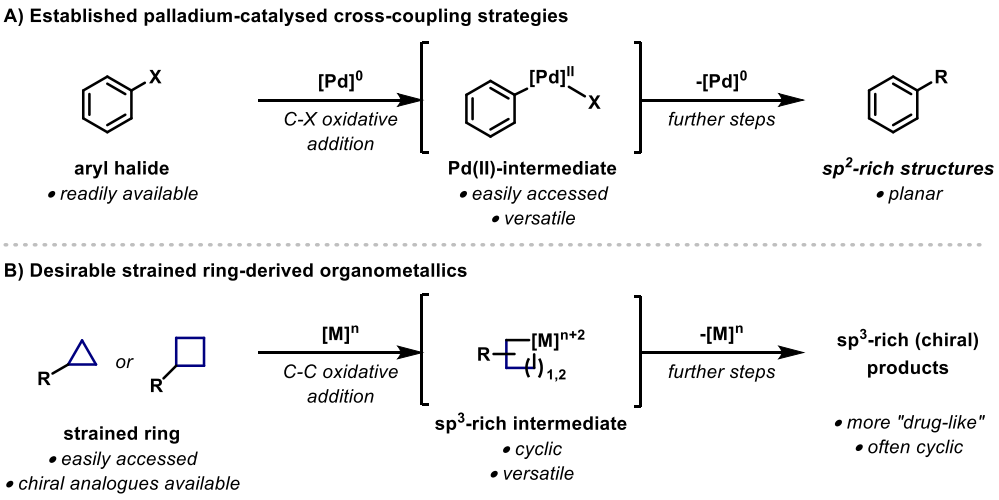
LG	leaving group
PMB	*para*-methoxybenzyl
rac	racemic
r.r.	regioisomeric ratio
SFC	supercritical fluid chromatography
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAB	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TMEDA	tetramethylethylenediamine
TMDSO	1,1,3,3-tetramethyldisiloxane

Chapter 1 – Introduction

1.1 Tackling the declining rate of drug discovery

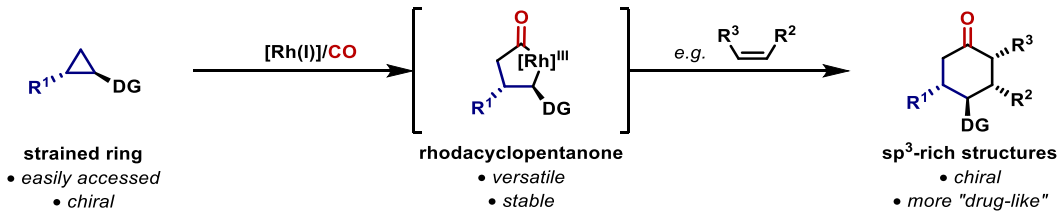
The modern pharmaceutical industry is unquestionably a success story in terms of its positive impact on improving health and driving medical innovation, but for small-molecule drug discovery programmes, high attrition rates remain a formidable challenge.[1,2] To help address this issue, the pharmaceutical sector has invested considerably in high throughput screening (HTS) methods to rapidly evaluate large libraries of drug candidates.[3] The shift to HTS practices has led to the identification of promising leads and the discovery of new drugs; however, efforts are often wasted pursuing structures that exhibit poor physiochemical properties.[4] In part, this is due to the reliance of medicinal chemists on adopting certain bond forming strategies,[5,6] and, within this context, palladium-catalysed cross-couplings[7] (*e.g.* the Suzuki-Miyaura reaction[8,9]) have evolved to become mainstay reactions in modern medicinal chemistry (Scheme 1A).[10] However, the widespread use of this type of strategy frequently leads to larger and more lipophilic compounds with high aromatic character, properties that are generally not conducive within drug discovery platforms.[11,12] Indeed, a recent study by Lovering and co-workers demonstrated that drug candidates possessing high fractional sp^3-character (Fsp^3), where Fsp^3 is defined as the fraction of sp^3 hybridised carbon atoms *vs.* the total number of carbon atoms, have a greater chance of transitioning through the drug discovery process and ultimately make it to the clinic.[13] Additionally, compounds with high Fsp^3 values often display improved binding affinities to their intended biological target and reduced off-target toxicity effects.[14]

Whilst the discovery of new drugs is an interdisciplinary challenge, synthetic chemistry can be the rate-determining step in the identification of new molecules that possess the necessary properties to become safe and efficacious drugs. Therefore, on the account of the above, there is a pressing need to escape from the sp^2-rich, planar structures generated from Pd(0)-catalysed cross-coupling reactions and, instead, a strategic desire to investigate sp^3-rich molecules in drug discovery campaigns. Stimulated by this challenge, synthetic chemists have embarked on several strategies; for example, C–C bond activation has emerged as a powerful tool for synthesising medicinally relevant scaffolds from relatively simple precursors. In particular, methodologies that exploit C–C oxidative addition of strained rings (*e.g.* cyclopropane or cyclobutane derivatives) have recently garnered significant attention from synthetic chemists as a means to generate sp^3-rich organometallics catalytically, which can then undergo further manipulations (*e.g.* migratory insertion of π-unsaturates followed by reductive elimination) to deliver sp^3-rich products (Scheme 1B).



Scheme 1: Comparison of a Pd(II)-intermediate with strained-ring derived organometallic.

In the Bower group, an extensive research programme has been undertaken to investigate the capacity of sp^3-metallacylic intermediates, with a strong focus on the generation and reactivity modes of rhodacyclopentanones.[15-24] Under Rh(I)-catalysed conditions, rhodacyclopentanones are generated by carbonylative C–C bond activation of cyclopropane precursors bearing a suitable directing group (Scheme 2). These versatile intermediates can be trapped by π-unsaturates or N- or C-based nucleophiles to deliver a diverse array of sp^3-rich, heterocyclic structures, many of which are found in medicinally important natural products and pharmaceutical reagents. Before presenting an overview of this strategy, a discussion on start-of-the-art examples of strain-driven C–C bond activation processes will be given.



Scheme 2: Formation of rhodacyclopentanones and target reactions with π-unsaturates.

1.2 Oxidative addition of transition metals into strained C–C bonds

Cyclopropane and cyclobutane derivatives play an important role in C–C bond activations as the release of ring strain facilitates metal insertion and provides a thermodynamic and kinetic driving force. Additionally, the HOMO and LUMO orbitals of cyclopropanes (and to a lesser extent cyclobutanes) have significant p-orbital character (due to the narrow bond angles within the cyclopropane ring) which makes them well-suited to bonding interactions with transition metal orbitals.[25] As such, the oxidative addition of transition metals into strained C–C bonds of 3- and 4-membered ring systems is a well-established process.[26-28] The first example of C–C oxidative addition into a cyclopropane was

reported by Tipper in 1955, which involved insertion of $PtCl_2$ into cyclopropane to deliver a platinacyclobutane.[29] Since this report, multiple classes of cyclopropane and cyclobutane derivatives have found wide utility in the development of metal-catalysed C–C bond activation methodologies (Figure 1).

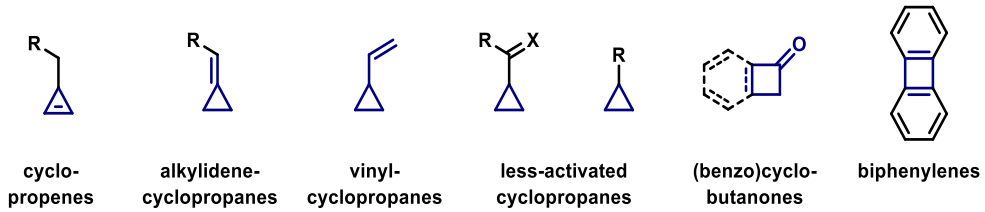


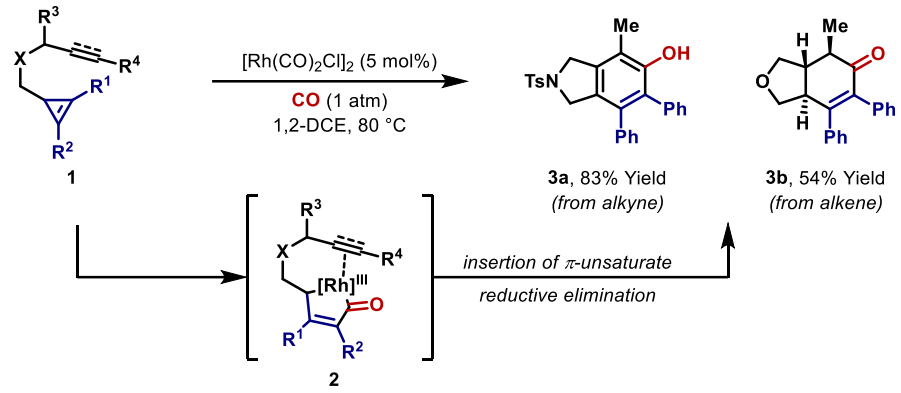
Figure 1: Categories of cyclopropanes and cyclobutanes employed in C–C oxidative addition processes.

In the following sections, examples of catalytic cycloadditions proceeding *via* oxidative addition to strained C–C bonds will be presented. The first part will cover cycloaddition processes involving cyclopropenes and alkylidenecyclopropane systems. The discussion will then focus on processes involving less-activated cyclopropanes, including aminocyclopropanes and cyclopropyl ketones, followed by selected methodologies based on C–C bond cleavage of cyclobutanones and benzocyclobutenones. Finally, in Section 1.3, an overview of processes developed previously in the Bower group will be presented. Whilst other classes of cyclopropane- and cyclobutane-based ring systems (*e.g.* vinylcyclopropanes,[28,30-33] and biphenylenes[28]) participate in cycloaddition processes, these will not be discussed as they fall outside the scope of the work contained in this thesis.

1.2.1 Multicomponent cycloaddition processes of cyclopropane-based systems

1.2.1.1 Cyclopropene-based systems

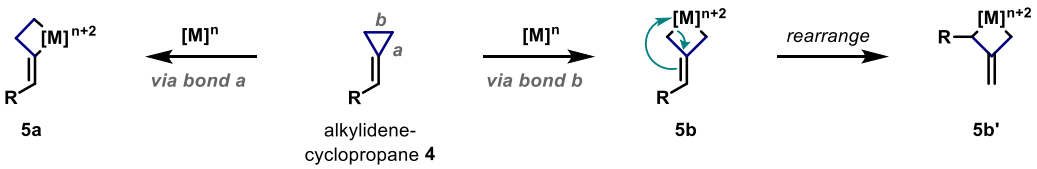
The internal unsaturation of cyclopropene rings renders them highly susceptible to C–C oxidative addition by transition metals. However, despite this propensity, few examples involving cyclopropenes exist in the literature, possibly due to the lack of flexible synthetic approaches targeting cyclopropene substrates. Notwithstanding this limitation, in 2010, Wang and co-workers published a Rh(I)-catalysed carbonylative (3+1+2) cycloaddition of cyclopropenes bearing pendant alkynes or alkenes to afford 5,6-bicyclic heterocycles (*e.g.* **3a** and **3b**) (Scheme 3).[34] It was proposed that the Rh(I)-catalyst inserts preferentially into the C–C single bond of **1**, and following migratory insertion of CO, provides rhodacyclopentenone **2**. From here, insertion of the tethered π-unsaturate, followed by C–C reductive elimination delivers the desired product. For processes involving alkenes (*e.g.* the formation of adduct **3b**), the transformation proceeded with high diastereoselectivity for the *trans*-ring junction.



Scheme 3: Rh(I)-catalysed carbonylative (3+1+2) cycloadditions of cyclopropenes with alkynes and alkenes.

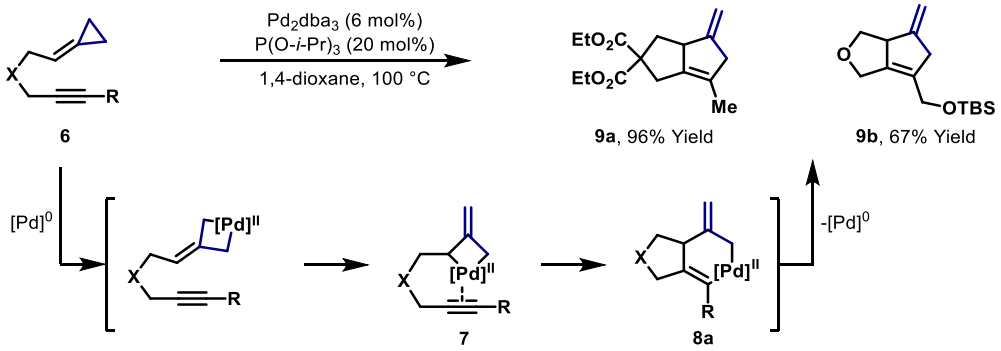
1.2.1.2 Alkylidenecyclopropane-based processes

Alkylidenecyclopropanes (ACPs) are another class of highly strained cyclopropane-based system which are reactive to C–C oxidative addition by transition metals (approximate strain energy of 39 *vs.* 55 kcal mol^{-1} for cyclopropenes).[35] For this substrate class, the metal can insert into either the proximal (*bond* ***a***) or distal (*bond* ***b***) C–C bond of alkylidenecyclopropane **4**, which leads to regioisomeric metallacycles **5a** and **5b** (Scheme 4). These metallacyclobutanes can be used directly or, in the case of **5b**, rearrangement can occur prior to engagement with a π-unsaturated component to give metallacycle **5b'**. In light of these scenarios, alkylidenecyclopropanes have emerged as highly versatile initiating motifs for cycloaddition reactions and interestingly, the mechanistic outcome of such reactions can be influenced by the choice of metal catalyst. In the following section, examples of processes involving selective metal insertion into either *bond* ***a*** or *bond* ***b*** of alkylidenecyclopropanes will be outlined.



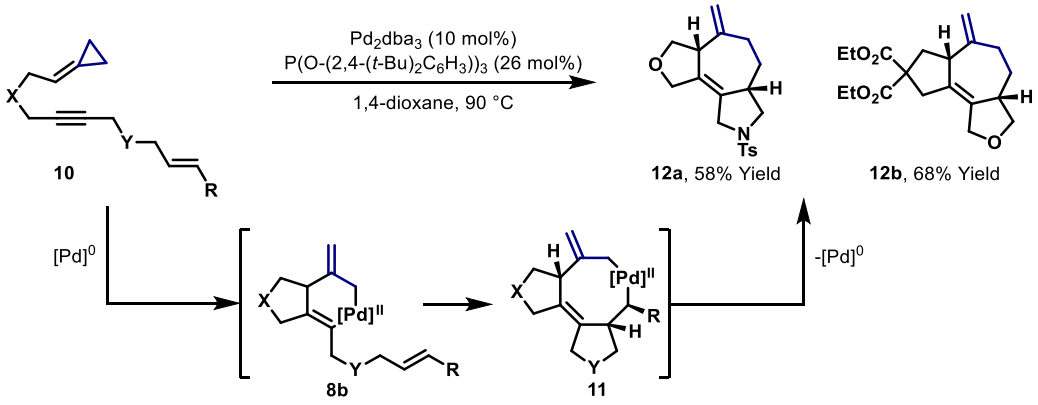
Scheme 4: Transition metal C–C bond insertion into alkylidenecyclopropanes.

In 2003, Mascareñas and co-workers developed a protocol for the Pd(0)-catalysed (3+2) cycloaddition of ACPs **6** with tethered alkynes to furnish bicyclic products (*e.g.* **9a** and **9b**) (Scheme 5).[36] Computational studies revealed that the most favourable reaction pathway involves initial insertion of the Pd(0)-catalyst into the distal bond of alkylidenecyclopropane **6**, from which subsequent isomerisation leads to complex **7**.[37] Next, alkyne carbometallation to 6-membered palladacycle **8a**, and C–C reductive elimination delivers the desired products **9a**–**b**. The Mascareñas group further expanded the methodology to include alkylidenecyclopropane substrates bearing other π-unsaturated functionalities, such as alkenes,[38] allenes[39] and 1,3-dienes,[40] which, in turn, allows flexible access to a range of ring systems.



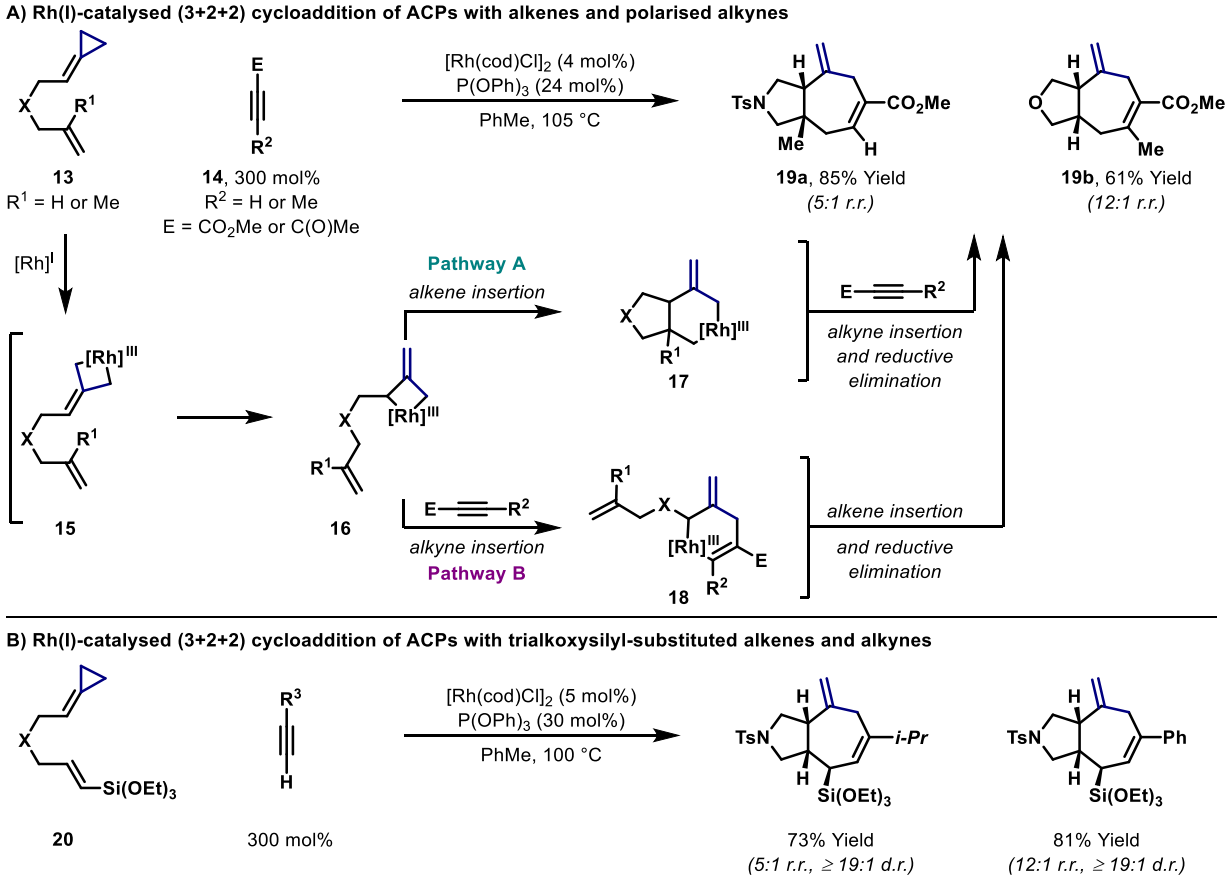
Scheme 5: Pd(0)-catalysed (3+2) cycloaddition of ACPs with tethered alkynes.

Notably, the same group reported that 6-membered palladacycle **8b** (*cf.* **8a**) could undergo a second carbometallation sequence prior to reductive elimination. For example, alkylidenecyclopropane **10**, containing an internal alkyne and a terminal alkene component, underwent (3+2+2) cyclisation to provide 5,7,5-tricycles (*e.g.* **12a** and **12b**) (Scheme 6).[41] In this transformation, palladacycle **8b** undergoes carbometallation of the pendant alkene (instead of reductive elimination) to form 8-membered palladacycle **11** and subsequent reductive elimination delivers the observed products **12a**–**b**. The authors noted that with the Pd(0)-catalyst, the system was prone to formation of (3+2) side-products (*via* reductive elimination from **8b**). To address this issue, a later study identified an upgraded Rh(I)-catalyst system, which, in turn, enabled chemoselective formation of the (3+2+2) cycloaddition adducts **12** in enhanced yields.[42] Computational studies were performed in order to account for the differences in reactivity for the Pd(0)- and Rh(I)-catalyst systems. It was found that, in the case of the Rh(I)-based system, the barrier for reductive elimination from the (3+2) intermediate (*cf.* palladacycle **8b**) is substantially higher in energy than that from the (3+2+2) intermediate (*cf.* palladacycle **11**).[42,43] This is in agreement with the experimental absence of the (3+2) cycloadducts **12**. In contrast, for the Pd(0)-based system, reductive elimination from palladacycle **8b** and carbopalladation of **8b** to **11** are competitive processes.



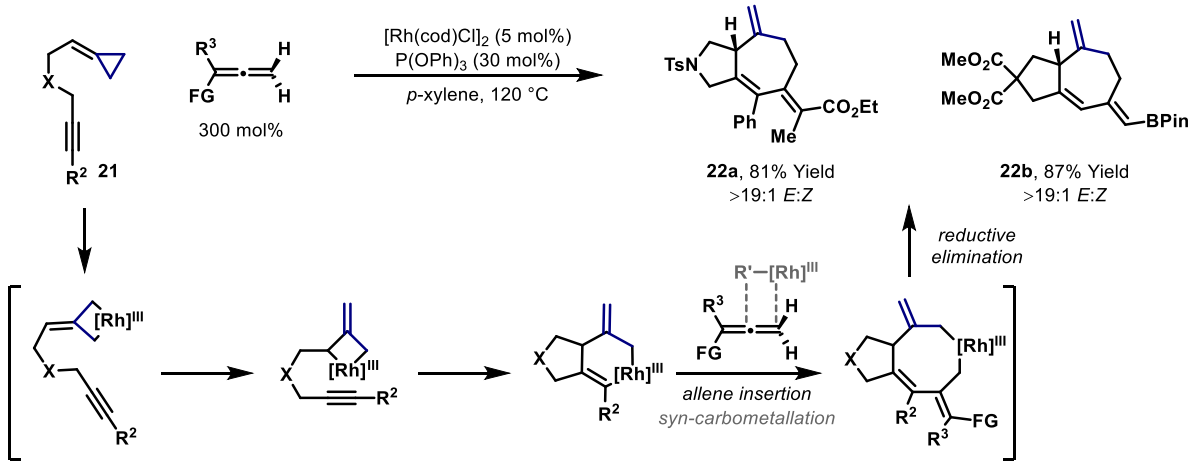
Scheme 6: Pd(0)-catalysed (3+2+2) cycloaddition of alkylidenecyclopropanes.

In 2008, Evans and Ingleby outlined a Rh(I)-catalysed intermolecular (3+2+2) cycloaddition of alkylidenecyclopropane **13** with exogenous electron-deficient alkynes **14** for the construction of *cis*-fused 5,7-bicycles (*e.g.* **19a** and **19b**) with high regiocontrol (5:1–12:1 r.r.) (Scheme 7A).[44] The authors postulated that bicycles **19a–b** are formed by an initial sequence involving oxidative addition of the Rh(I)-catalyst into the distal C–C bond of **13**, followed by rearrangement of **15** to rhodacyclobutane **16**. From this central intermediate, the mechanism diverges depending on the order of insertion of the π-unsaturated components. In pathway A, insertion of the tethered alkene to **17** is followed by insertion of the alkyne component and reductive elimination to afford products **19a**–**b**. Alternatively, in pathway B, alkyne insertion into **16** affords rhodacyclohexene **18**. Subsequent insertion of the alkene unit and reductive elimination delivers products **19a**–**b**. Moreover, this method provides concise access to structural motifs that are found in several natural products. To demonstrate its utility, Evans and Ingleby successfully applied this methodology to the three-step total synthesis of the sesquiterpene, pyrovellerolactone.[45] However, despite this application, a potential drawback of this methodology is that it is limited to electron-poor alkynes (*i.e.* the E substituent of **14** = CO_2Me or C(O)Me). To address this shortcoming, a subsequent report disclosed that the introduction of a triethoxysilyl group on the alkene unit of alkylidenecyclopropane **20** improves the scope of the (3+2+2) cycloaddition to include non-activated alkynes (Scheme 7B).[46]



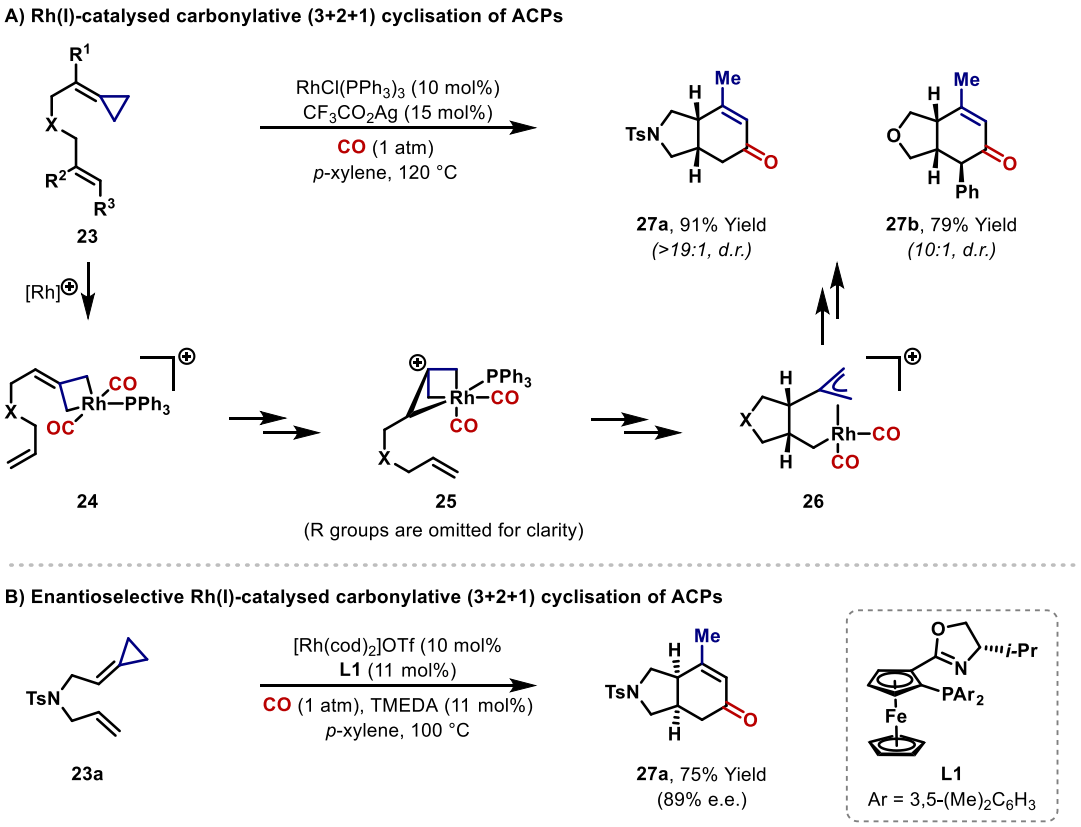
Scheme 7: Rh(I)-catalysed (3+2+2) cycloaddition of alkylidenecyclopropanes with alkynes and alkenes.

In a later report, Evans and co-workers detailed an intermolecular Rh(I)-catalysed (3+2+2) cycloaddition of alkylidenecyclopropanes **21** and exogenous substituted allenes to provide 5,7-bicyclics bearing tri- and tetrasubstituted exocyclic olefins (*e.g.* **22a** and **22b**) (Scheme 8).[47] By inserting an additional methylene spacer in the alkyne tether, the scope was extended to include 6,7-heterocycles (not depicted). The authors proposed that the geometry of the substituted exocyclic alkene unit is controlled by preferential *syn*-carbometallation of the less hindered face of the terminal allene π-bond.



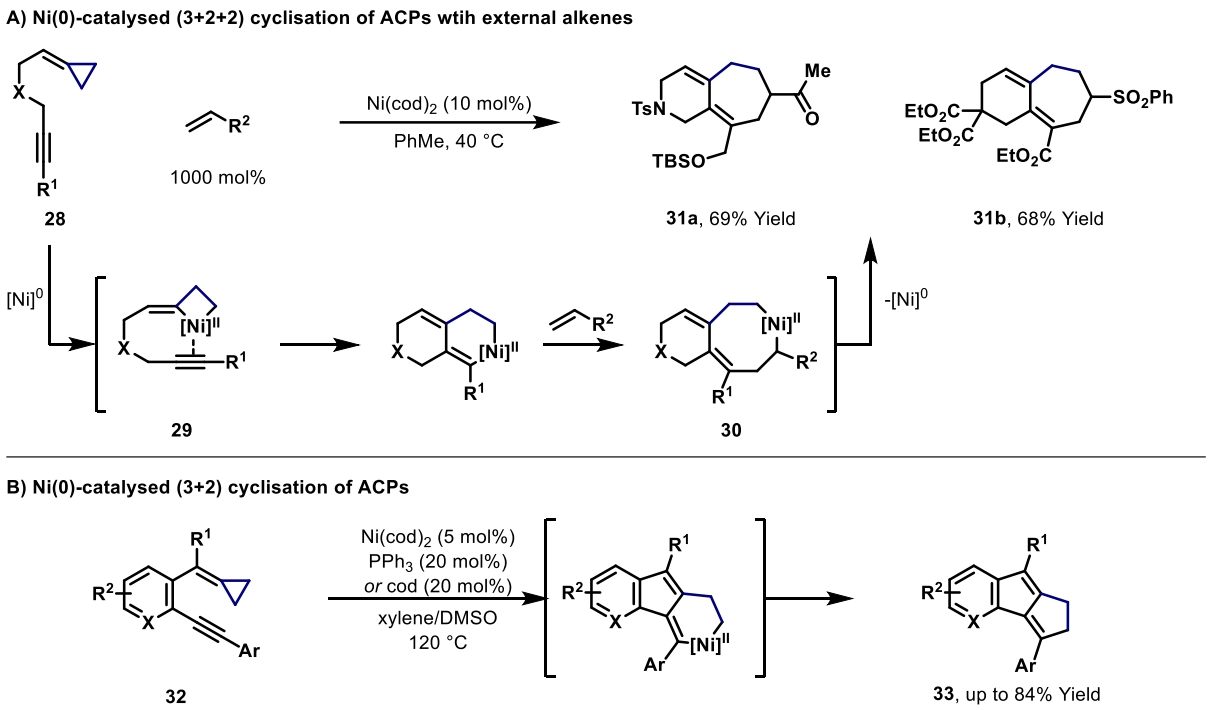
Scheme 8: Rh(I)-catalysed (3+2+2) cyclisation of alkylidenecyclopropanes with external allenes.

In 2012, Evans and co-workers disclosed Rh(I)-catalysed (3+1+2) cycloadditions of alkylidenecyclopropanes **23** with carbon monoxide to form *cis*-fused bicyclohexenones (*e.g.* **27a** and **27b**) in excellent yield and high diastereocontrol (Scheme 9A).[48] Computational studies support a mechanistic pathway proceeding *via* insertion of the Rh-CO complex into the distal bond of **23** to give rhodacycle **24**, followed by isomerisation to complex **25**. From here, alkene insertion to η^3-allyl species **26** is followed by a sequence comprising of migratory insertion of CO, C–C reductive elimination and alkene isomerisation to afford products **27a**–**b**. Preliminary studies using $[Rh(cod)_2]OTf$ in combination with a chiral *P*,*N*-ligand **L1** gave rise to good levels of enantioselectivity (*e.g.* 89% e.e. for **27a**) (Scheme 9B). Later in 2014, Kim and Chung reported a related protocol in which Rh(I)-catalysed carbonylative (3+1+2) cycloaddition of ACPs with tethered alkynes generated bicyclic phenol derivatives.[49]



Scheme 9: Rh(I)-catalysed carbonylative (3+1+2) cycloadditions of alkylidenecyclopropanes and computationally supported mechanism.

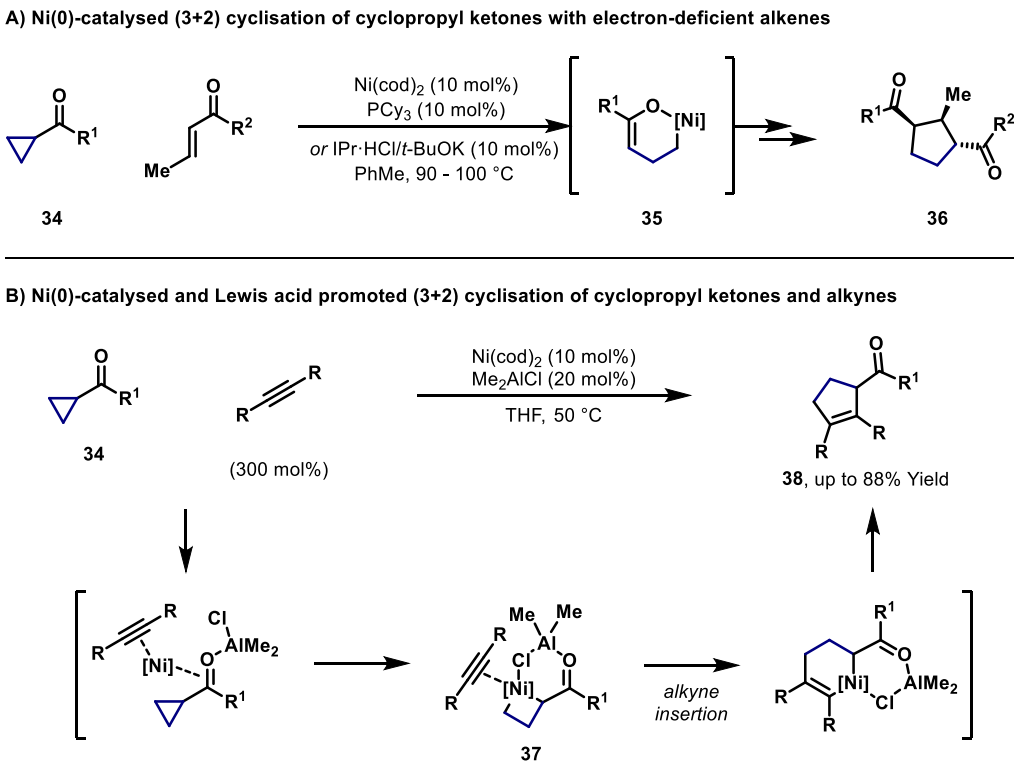
More recently, interest in the development of complementary processes that utilise Ni(0)-catalysts has grown rapidly, particularly as Ni(0)-catalysts behave differently to Pd(0)- and Rh(I)-catalysts. Indeed, as early as the 1970s it was shown that Ni(0)-catalysts generally insert into the proximal C–C bond of alkylidenecyclopropanes (*i.e. bond* ***a*** of **4**, Scheme 4), instead of into the distal bond (*i.e. bond* ***b*** of **4**, Scheme 4).[50,51] This preference is in contrast to the Pd(0)- and Rh(I)-catalysed processes discussed so far and, as a result, presents the opportunity for identical alkylidenecyclopropane precursors to be transformed into different ring systems depending on the choice of catalyst employed. Mascareñas first exploited this effect to promote the formation of 6,7-fused bicycles (*e.g.* **31a** and **31b**) by a Ni(0)-catalysed (3+2+2) cycloaddition of alkylidenecyclopropane **28** with external alkenes (Scheme 10A).[52] Computational studies indicate the Ni(0)-catalyst is directed into the proximal bond of alkylidenecyclopropane **28** by the tethered alkyne unit. The resulting nickelacycle **29** undergoes consecutive alkyne and alkene carbometallation to give intermediate **30**, which upon reductive elimination affords the 6,7-bicyclic products. Subsequent reports have highlighted the versatility of nickelacycles related to **28**; for example, in 2014, the Mascareñas group reported a Ni(0)-catalysed intramolecular (3+2+2) cycloaddition of ACPs with tethered alkenes and alkynes to provide tricyclic ring systems (*cf.* Scheme 6).[53] Additionally, Zhang and co-workers detailed the synthesis of aryl-fused products **33** *via* cleavage of the proximal bond of ACPs **32** under Ni(0)-catalysis (Scheme 10B).[54]



Scheme 10: Ni(0)-catalysed cycloadditions of ACPs.

1.2.1.3 Cyclopropyl ketone/imine-based processes

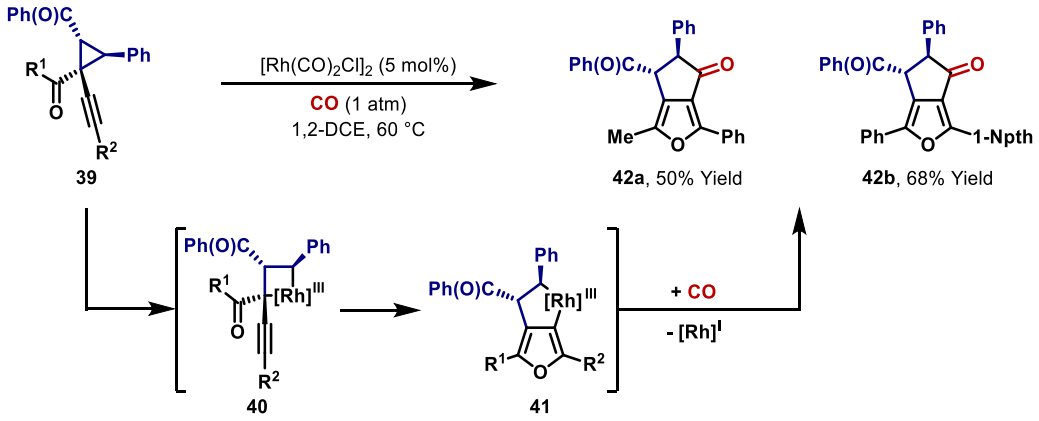
The examples discussed so far highlight notable progress in processes involving C–C cleavage of cyclopropanes possessing fused or adjacent C-based π-unsaturation. In addition to these achievements, significant interest has also been directed towards processes involving C–C bond activation of cyclopropanes bearing electron-withdrawing π-unsaturation, such as cyclopropyl ketones,[55-57] cyclopropyl imines[58-60] and cyclopropylamides.[61] From a synthetic viewpoint, these substrates are appealing because substituted analogues are, in most cases, easily accessible and often in enantioenriched form. In 2006, Liu and Montgomery,[55] and Ogoshi and co-workers[57] independently reported the Ni(0)-catalysed cycloaddition of cyclopropyl ketones (*e.g.* **34**) and alkenes to give substituted cyclopentanes (*e.g.* **36**) (Scheme 11A). In these examples, 6-membered oxanickelacycle **35** was identified as a key intermediate, which following intermolecular conjugate addition to the enone species and reductive elimination, affords cyclopentane **36**.



Scheme 11: Ni(0)-catalysed (3+2) cycloadditions of cyclopropylketones

In 2011, Ogoshi and co-workers extended the methodology to include alkynes, and in this case, the inclusion of a Lewis-acidic organoaluminium co-catalyst was necessary to facilitate the formation of cyclopentene products **40** (Scheme 11B).[62] The authors proposed that Me_2AlCl activates the ketone which, in turn, facilitates coordination of an alkyne-ligated Ni(0)-complex and enables C–C oxidative addition to give nickelacyclobutane **37**. Key intermediate **37** is stabilised by a Ni–Cl interaction that prevents isomerisation to a 6-membered nickelacycle (*cf.* **35**). Migratory insertion of the external alkyne into **37** is followed by reductive elimination to deliver cyclopentene **38**.

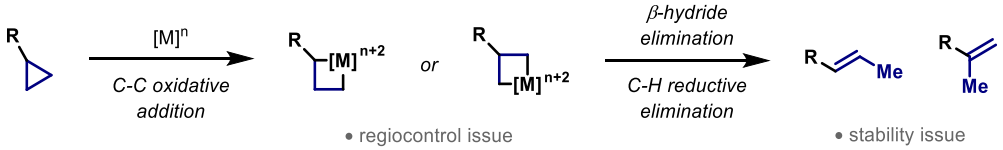
Alongside these advancements, additional studies have shown that other metals, including Rh and Pd,[63] insert into cyclopropyl ketones. In 2009, Zhang and co-workers disclosed the Rh(I)-catalysed carbonylative cyclisation of propargylic cyclopropyl ketones **39** to form furan-fused cyclopentanones (*e.g.* **42a** and **42b**) (Scheme 12).[64] The proposed mechanism proceeds *via* regioselective C–C oxidative addition of the Rh(I)-catalyst into the proximal C–C bond of **39** to give rhodacyclobutane **40**. Rearrangement of **40** to rhodacycle **41**, followed by insertion of CO and reductive elimination affords the observed products **42a**–**b**.



Scheme 12: Carbonylative rearrangement of alkynyl cyclopropyl ketones.

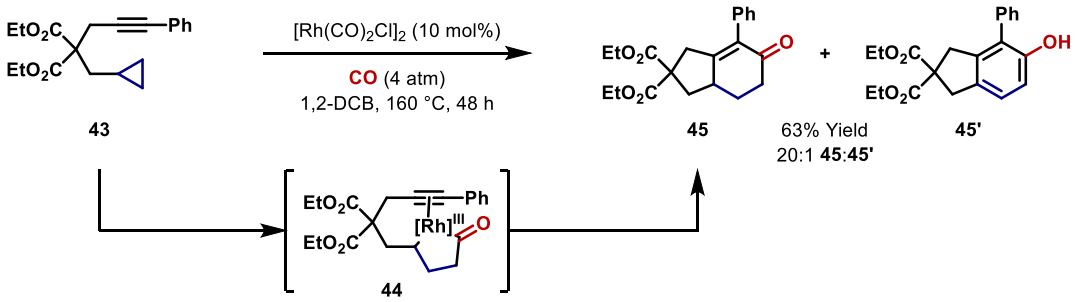
1.2.1.4 Directed metal-addition to non-activated cyclopropanes

In contrast to the processes discussed above, examples of metal-catalysed cycloadditions of non-activated cyclopropanes have been slow to emerge.[26,65] For such systems, an extra layer of complexity arises due to issues regarding regioselectivity of C–C oxidative addition and metallacyclobutane stability (Scheme 13).



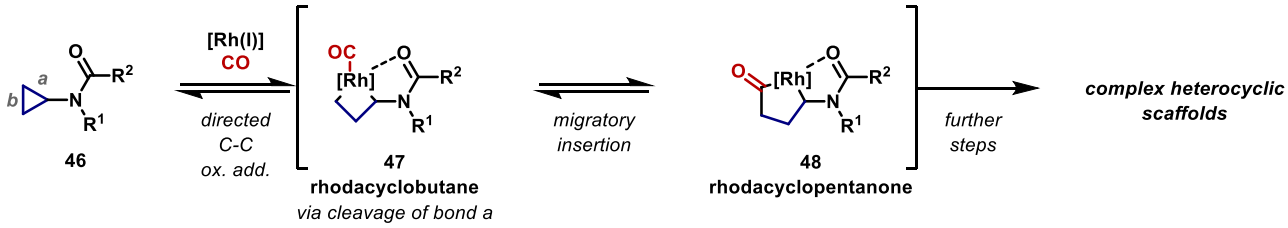
Scheme 13: Metal-catalysed C–C bond activation of non-activated cyclopropanes.

The issue of stability outlined in Scheme 13 can be eased by fast capture of the metallacyclobutane with carbon monoxide to provide a relativity stable metallacyclopentanone. This carbonylative strategy was first detailed by Wilkinson and co-workers in 1968, in which exposure of cyclopropane to $[Rh(CO)_2Cl]_2$ resulted in ring expansion to deliver a monomeric phosphine-bound rhodacyclopentanone.[66] Building upon this discovery, Koga and Narasaka disclosed that the Rh(I)-catalysed (3+1+2) cycloaddition of cyclopropane **43** with a tethered alkyne and carbon monoxide generated bicyclic cyclohexanone **45** in good yield and high selectivity (63% yield, 20:1, **45**:**45'**) (Scheme 14).[67] The reaction was proposed to proceed *via* rhodacyclopentanone **44**, which derives from insertion of the Rh(I)-catalyst into the more hindered C–C bond of **43**. Additionally, in this process, the authors proposed that the regioselectivity is controlled by coordination of the Rh(I)-catalyst to the tethered alkyne component. From rhodacyclopentanone **44**, migratory insertion of the alkyne unit and reductive elimination affords product **45**. Shortcomings of this approach include the requirement for a high pressure of carbon monoxide and high reaction temperatures; therefore, protocols that can overcome these limitations and enable efficient and selective access to related metallacyclic intermediates are highly sought after.



Scheme 14: Rh(I)-catalysed carbonylative (3+1+2) cycloaddition of cyclopropane with a tethered alkyne.

With these issues in mind, in 2013 the Bower group demonstrated the regioselective generation of amino-rhodacyclopentanones from aminocyclopropanes by employing an *N*-directing group strategy (Scheme 15).[15] The strategy utilises a carbonyl-based directing group to promote regioselective oxidative addition of a Rh(I)-catalyst into the proximal *bond **a*** of aminocyclopropane **46**. From here, migratory insertion of carbon monoxide into the resulting rhodacyclobutane **47** delivers rhodacyclopentanone **48**. Importantly, it has been shown that the steps leading up to rhodacyclopentanone **47** are reversible. The ability to access rhodacyclopentanones both selectively and efficiently has provided a general platform from which a range of downstream catalytic transformations have been developed. A detailed overview of this carbonylative ring expansion strategy is presented in Section 1.3.

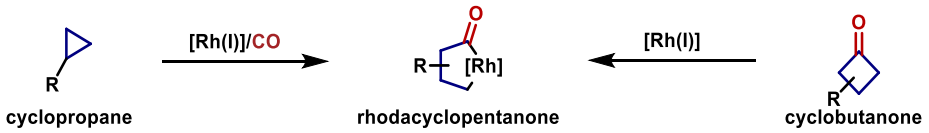


Scheme 15: Rh(I)-catalysed carbonylative ring expansion of aminocyclopropanes.

1.2.2 Multicomponent cycloadditions of cyclobutane-based systems

Significant efforts have also been devoted to the development of metal-catalysed strain-driven C–C bond activations of cyclobutane-based substrates and, within this field, cyclobutanone and benzocyclobutenones have emerged as privileged substrates.[68] In 1994, pioneering work by Ito and Murakami demonstrated that Rh(I)-catalysts insert into the less hindered acyl–C(sp^3) bond of cyclobutanone derivatives, a strategy which offers an alternative entry to rhodacyclopentanones (Scheme 16).[69] Since this seminal publication, rhodacyclopentanones generated from cyclobutanones and benzocyclobutenones have been exploited by a number of research groups to access diverse hetero- and carbocycles and, in certain cases, this has been achieved enantioselectively.[27,70] In general, oxidative addition of Rh(I)-catalysts into cyclobutanones occurs at the weaker acyl–C(sp^2) bond over the comparatively stronger C(sp^3)–C(sp^3) bond. In the following section, significant advances of

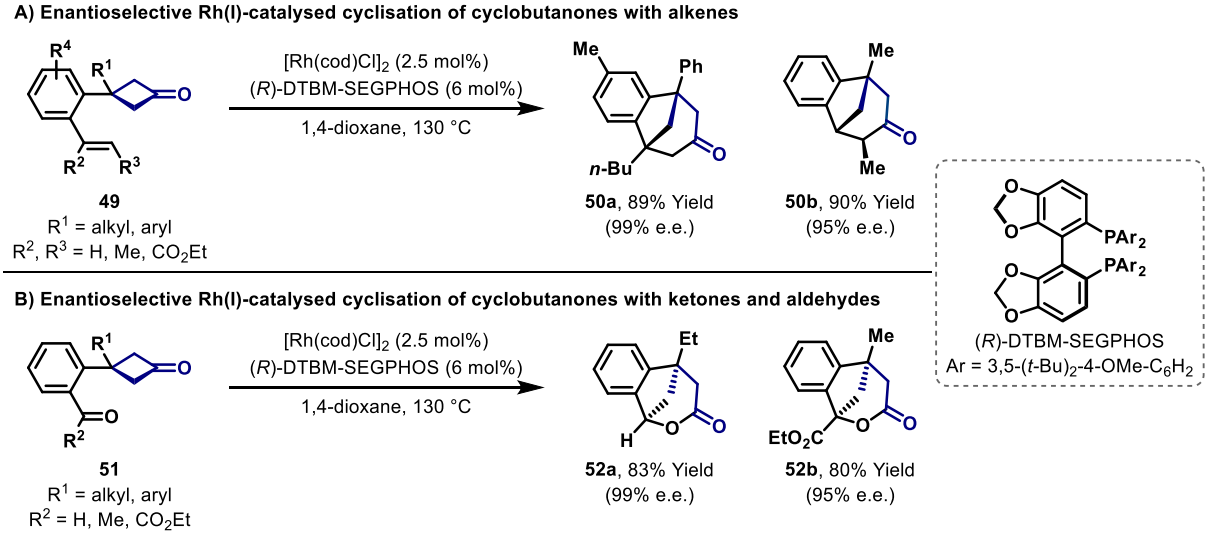
cyclobutanone- and benzocyclobutenone-derived rhodacyclopenta(e)nones (and related metallacyclopentanones) will be outlined.



Scheme 16: Alternative entry to rhodacyclopentanones from cyclobutanones.

1.2.2.1 Cyclobutanone-based processes

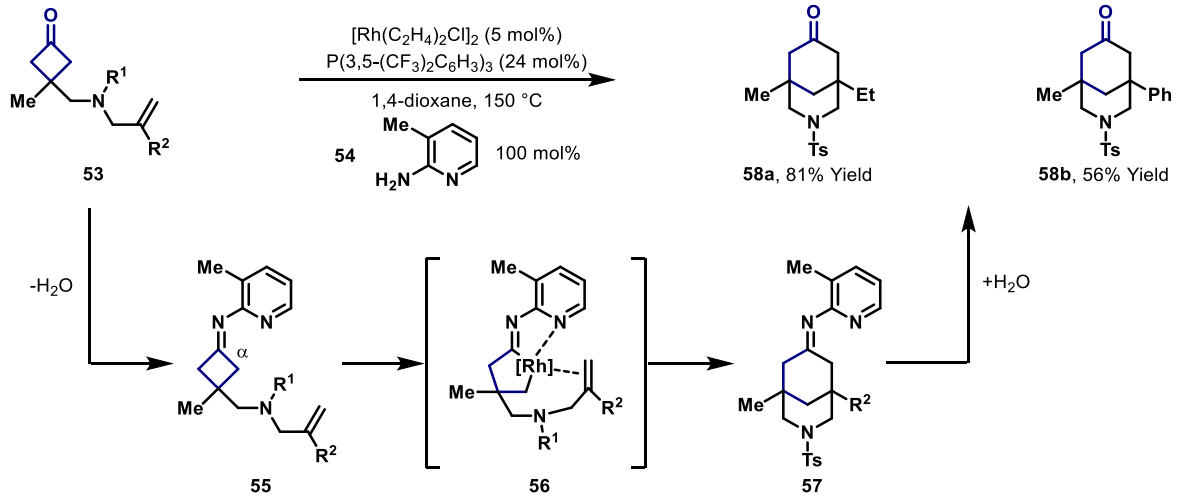
In 2014, Cramer and co-workers disclosed the enantioselective synthesis of benzofused bicyclic ketones (*e.g.* **50a** and **50b**) from cyclobutanones **49** using a $[Rh(cod)Cl]_2$/(*R*)-DTBM-SEGPHOS catalyst system (Scheme 17A).[71,72] In this transformation, oxidative addition of the Rh(I)-catalyst into the acyl–C(sp^3) bond of cyclobutanone **49** is the enantiodetermining step. Migratory insertion of the tethered alkene into the resulting rhodacyclopentanone, followed by reductive elimination provides ketones **50a** and **50b**. In a subsequent report, Cramer extended the cycloaddition strategy to cyclobutanones bearing tethered carbonyls to afford bridged lactones (*e.g.* **52a** and **52b**) in high yield and enantioselectivity (*e.g.* 83% yield and 99% e.e. for **52a**) (Scheme 17B).[73] The same fundamental mechanistic steps for this substrate class were invoked as for the cyclobutanone **49**. Of note, this protocol is significant for its complete selectivity for C–C bond activation over insertion of the Rh(I)-catalyst into the aldehydic C–H bond (*i.e.* aldehydic C–H bond of cyclobutanone **51**, R^2 = H).



Scheme 17: Enantioselective C–C bond activation of cyclobutanones.

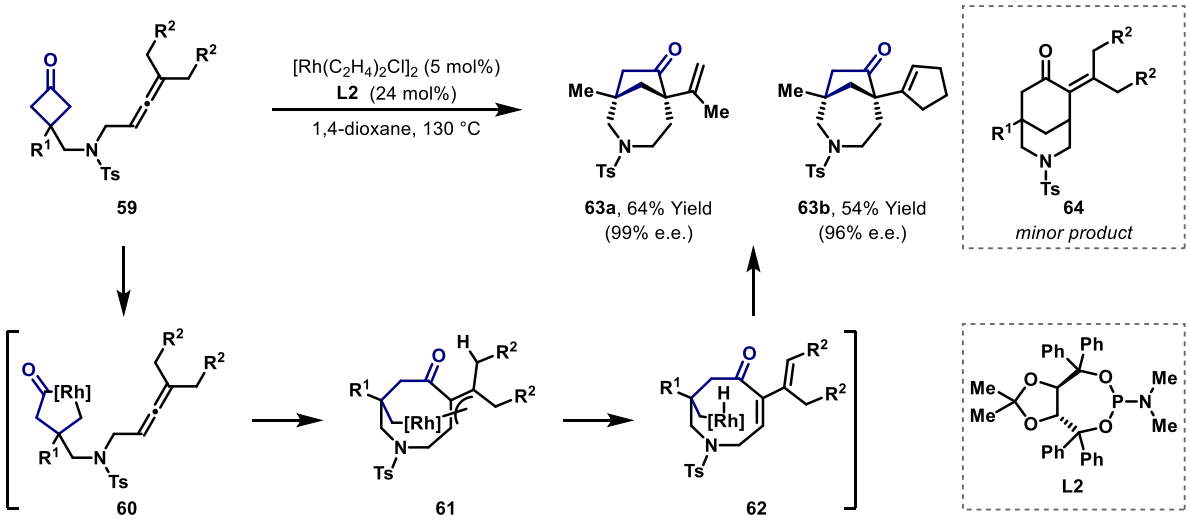
For certain catalytic processes, competing decarbonylation from the key rhodacyclopentanone intermediate can be a major side-reaction that leads to undesired ring contractions or fragmentation pathways.[74] To side-step this deleterious pathway, the Dong group utilised a temporary directing group strategy in the Rh(I)-catalysed (4+2) cycloaddition of cyclobutanones **53** to provide *N*-heterobicyclic

ketones (*e.g.* **58a** and **58b**) (Scheme 18).[75] Inspired by previous reports by Jun and co-workers,[76,77] treatment of cyclobutanone **53** with 2-amino-3-methylpyridine **54** results in the *in situ* formation of imine **55**, which then directs insertion of the Rh(I)-catalyst into the α-bond of cyclobutanone **55** by forming a chelation complex with the metal. Subsequent migratory insertion of the alkene unit into **56**, followed by reductive elimination installs the bridged scaffold to give intermediate **57**. Finally, hydrolysis of imine **57** affords the [3.3.1]-bridged ketone products **58a**/**b**. Note that rhodacycle **56** cannot undergo decarbonylation. Recently, in 2020 the Dong group reported a notable extension of this (4+2) cycloaddition by replacing the alkene component of **53** with an alkyne unit, which, in turn, enabled access to chiral [3.3.1]-bridged bicyclic products.[78] The authors reported that high enantioselectivities can be achieved by employing cationic $[Rh(cod)_2]NTf_2$ and (*R*)-DTBM-SEGPHOS, and more significantly, for this new transformation, the imine-protecting group was no longer required.



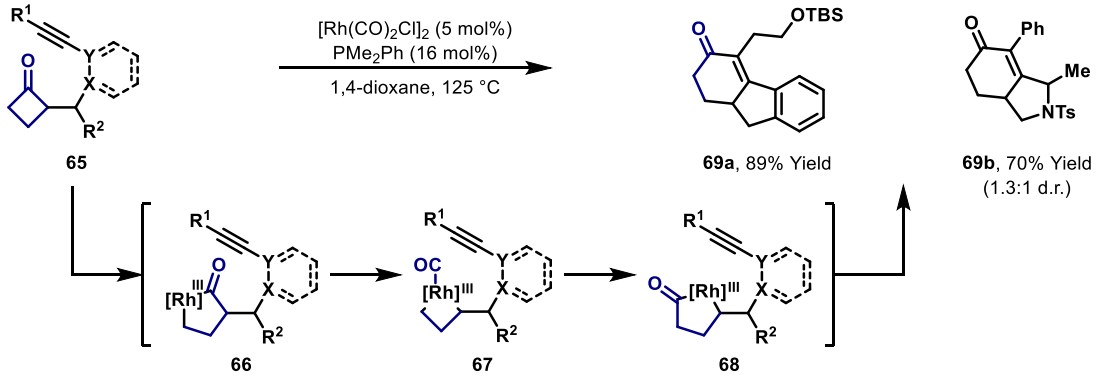
Scheme 18: Imine-directing group strategy to avoid decarbonylation of cyclobutanones.

In a related publication, Dong and co-workers reported the combination of $[Rh(CH_2H_4)Cl]_2$ and chiral TADDOL-derived phosphoramidite ligand (**L2**) effects the enantioselective (4+1) cyclisation of cyclobutanone **59** bearing a pendant allene to provide [4.2.1]-bicyclic ketones (*e.g.* **63a** and **63b**) in good yields and enantioselectivities (*e.g.* 99% e.e. for **63a**) (Scheme 19).[79] In this transformation, generation of rhodacyclopentanone **60** is followed by migratory insertion of the allene unit to give π-allyl intermediate **61**. From here, β-hydride elimination to enone **62** is followed by hydrometallation and reductive elimination to give the observed product **63**. The proposed mechanism was supported by deuterium-labelling studies. Interestingly, the [3.3.1]-bicyclic product **64** (formed *via* reductive elimination from intermediate **60**) was observed only in small quantities.



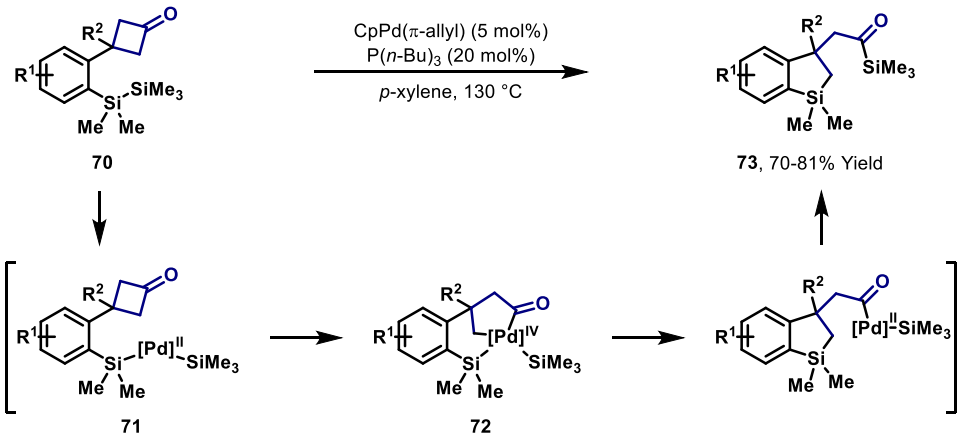
Scheme 19: Rh(I)-catalysed allene insertion into cyclobutanones.

Further exemplary work by Dong described the Rh(I)-catalysed (4+2) cycloaddition of unsymmetrical cyclobutanones **65** with tethered alkynes to generate fused-cyclohexanones (*e.g.* **69a** and **69b**) (Scheme 20).[80] The regioselectivity of the initial metal addition step was investigated by ^{13}C-labelling studies, which revealed a preference for the Rh(I)-catalyst to insert into the less-hindered distal C(acyl)–C(sp^3) bond of **65**. The resulting rhodacyclopentanone **66** isomerises *via* decarbonylation to give rhodacyclobutane **67**, which then undergoes CO reinsertion at the less hindered alkyl position to provide rhodacyclopentanone **68**. From here, alkyne carbometallation and reductive elimination affords the observed products **69a–b**.



Scheme 20: Rh(I)-catalysed alkyne insertion into cyclobutanones *via* a decarbonylation/carbonylation sequence.

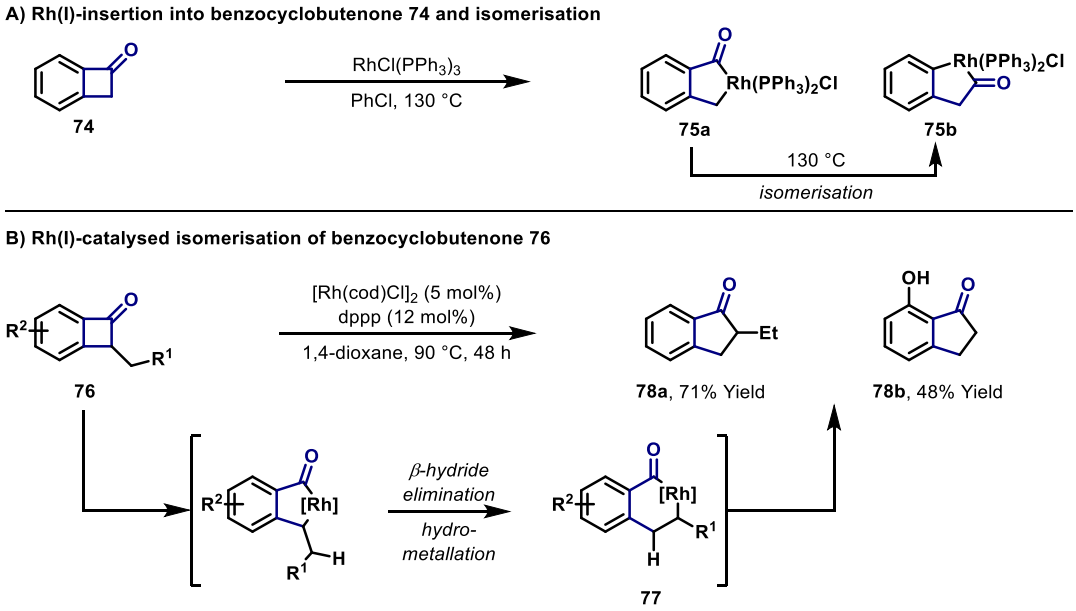
In contrast to the preceding examples, recent contributions by Murakami and co-workers have shown that conversion of cyclobutanone **70** to acyl silane **73** is possible by employing a Pd(0)-catalyst system (Scheme 21).[81] Mechanistic studies indicated that the transformation is initiated by Pd(0)-addition to the Si–Si bond of cyclobutanone **70** to give Pd(II)-intermediate **71**. This key intermediate then triggers C–C bond activation of the cyclobutanone moiety, which generates Pd(IV)-complex **72**. From here, consecutive C–Si/acyl–Si reductive eliminations deliver acyl silane **73**.



Scheme 21: Pd-catalysed cyclobutanone C–C bond activation by initial insertion into a Si-Si bond.

1.2.2.2 Benzocyclobutenone-based processes

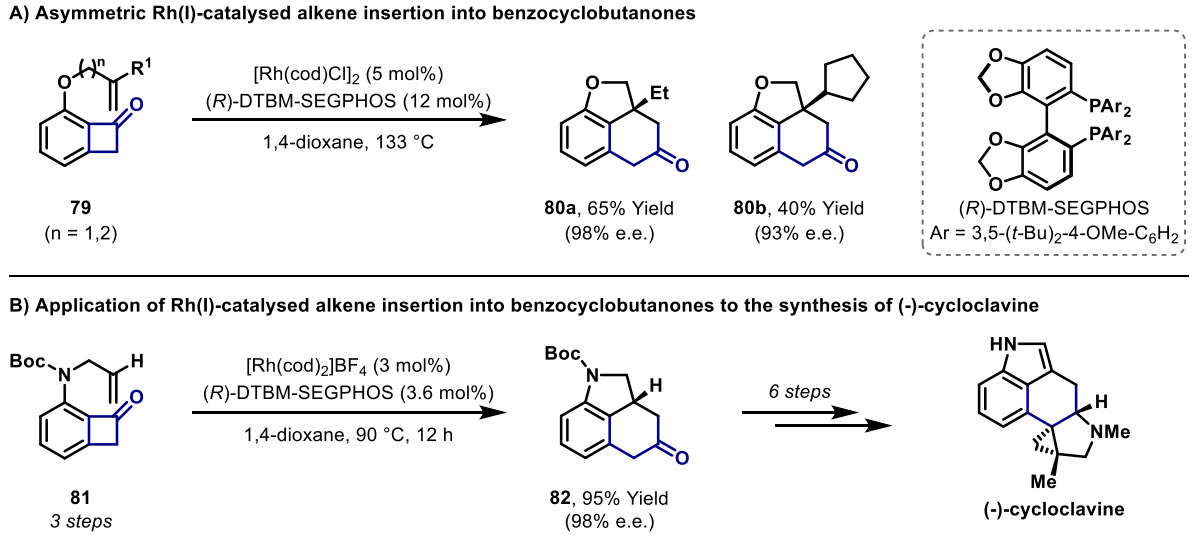
The processes discussed so far in this section are all triggered by insertion of a metal catalyst into the C(acyl)–C(sp^3) of a cyclobutanone derivative. Alongside these advancements, it has also been shown that rhodacycloindanones can be derived from benzocyclobutenone precursors. Seminal work by Liebeskind demonstrated that Wilkinson's catalyst can insert into the C(sp^3)–acyl bond of benzocyclobutenone **74** to provide rhodacycloindanone **75a**, which isomerises to the more stable regioisomer **75b** upon heating (Scheme 22A).[82] Later in 2015, computational studies revealed that isomerisation likely occurs by a retrocarbonylation/carbonylation sequence, rather than by reversible oxidative addition.[83]



Scheme 22: Formation of rhodacycloindanones and related catalytic processes.

In recent years, the Dong group has capitalised upon the formation of benzocyclobutenone-derived rhodacyclopentenones for the development of several Rh(I)-catalysed

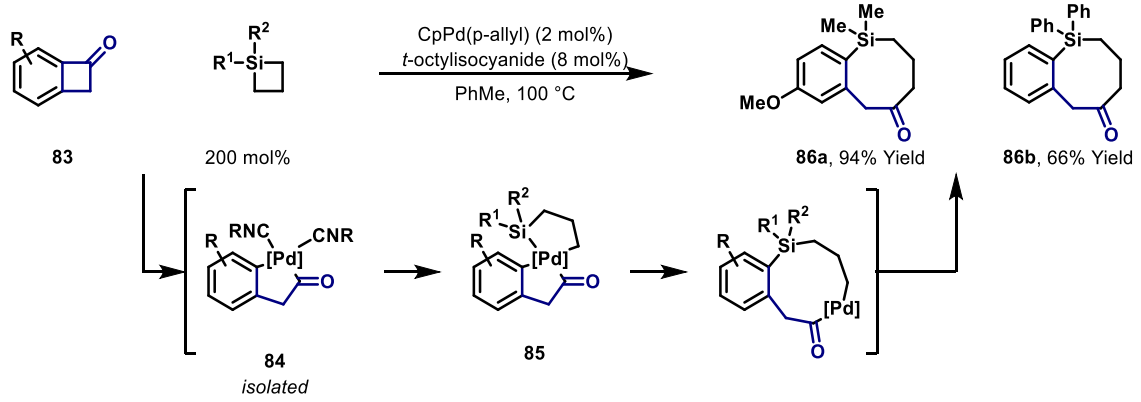
intramolecular cyclisations. Early studies demonstrated that exposure of benzocyclobutenones **76** to phosphine-ligated Rh(I)-systems resulted in isomerisation to benzocyclopentenones (*e.g.* **78a** and **78b**) (Scheme 22B).[84] Mechanistic experiments and computational studies support a pathway involving Rh(I)-insertion into the less-substituted acyl–C(sp^3) bond of **76**, followed by β-hydride elimination and hydrometallation to rhodacycle **77**, from which reductive elimination delivers the observed products.[85] Later in 2012, Dong and co-workers reported the regio- and enantioselective Rh(I)-catalysed cyclisation of benzocyclobutenones **79** bearing tethered alkenes to generate complex tricyclics (*e.g.* **80a** and **80b**) in moderate yield and high enantioselectivity (*e.g.* 63% yield and 98% e.e. for **80a**) (Scheme 23A).[86,87] Interestingly, the resulting product **80a**/**b** can be reduced to the corresponding saturated tricycle under Rh(I)-catalysed hydrogenative conditions. The utility of this process was showcased in the asymmetric total synthesis of (–)-cycloclavine and (–)-5-*epi*-cycloclavine (Scheme 23B).[88] In this approach, allylaniline **81** (prepared in three steps) underwent Rh(I)-catalysed cyclisation to secure the fused-tricyclic core of key intermediate **82** in 95% yield and 98% e.e. This intermediate was then elaborated to the target molecule in a further 6 steps. Additionally, related processes involving the insertion of alternative π-unsaturated units, including alkynes,[89] acrylamides,[90] ketones[91] and oximes,[92] into benzocyclobutenone-derived rhodacyclopentenones have been reported.



Scheme 23: Synthesis of tricyclic heterocycles *via* Rh(I)-catalysed cycloadditions of benzocyclobutenones.

Contrary to these aforementioned processes, in 2017 Murakami outlined a Pd(0)-catalysed intermolecular cross metathesis of benzocyclobutenone **83** with silacyclobutane to form benzofused 8-membered silacycles (*e.g.* **86a** and **86b**) (Scheme 24).[93] Of note, optimisation studies identified *t*-octyl isocyanide as a crucial additive; this led to the isolation of palladacyclopentenone **84**, which was shown to be catalytically active in the transformation. Computational studies support a mechanism involving two sequential oxidative additions and two subsequent reductive eliminations. The initial oxidative addition cleaves the C(aryl)–C(acyl) bond of benzocyclobutenone **83** to generate

palladacyclopentenone **84**. The second oxidative addition with silacyclobutane leads to Pd(IV)-complex **85**. This intermediate then undergoes consecutive C–Si and C(acyl)–C reductive eliminations to produce the observed products **86a**/**b**.[94]



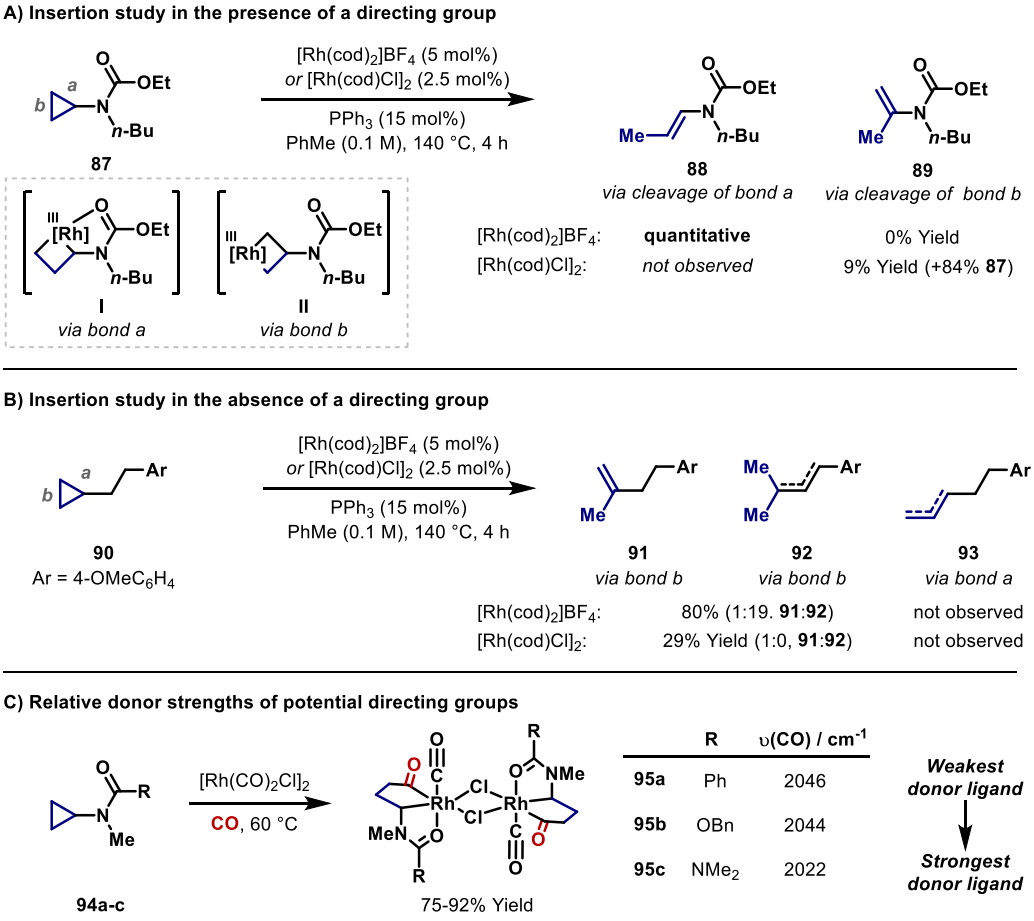
Scheme 24: Pd(0)-catalysed intermolecular coupling of benzocyclobutanones and silacyclobutanes.

The processes outlined in this introduction not only highlight notable achievements in metal-catalysed C–C bond activation of cyclopropane and cyclobutane derivatives, but also illustrates the diverse range of sp^3-rich structures that can be accessed by adopting this approach. The varied reactivity modes of these sp^3-rich metallacycles towards π-systems, combined with the ability to create a chiral environment, enables previously inconceivable molecular disconnections, which, in turn, facilitates the rapid synthesis of natural products and pharmaceutically relevant scaffolds. In particular, recent years have witnessed steady advances in applying this strain-release approach towards the synthesis of medium-sized ring systems. With this primary objective in mind, the research contained in this thesis concerns the synthesis of various 7- and 8-membered (poly)heterocycles *via* Rh(I)-catalysed carbonylative ring expansion of aminocyclopropane precursors. As an introduction to the research contained in the following chapters, key aspects of prior cycloaddition processes developed in the Bower group that are based upon Rh(I)-addition to aminocyclopropanes will now be presented.

1.3 A directing group strategy for the generation of rhodacyclopentones

In 2013, the Bower group initiated a research programme into the carbonylative C–C bond activation of aminocyclopropanes. As stated previously, critical to the success of this strategy was the regioselective generation of the requisite rhodacyclopentanone intermediate (see Scheme 15). Preliminary insertion studies revealed that exposure of carbamate-protected aminocyclopropane **87** to a cationic Rh(I)-source, under an atmosphere of argon, afforded linear alkene **88** as the sole product (Scheme 25A).[15] Presumably formation of alkene **88** arises *via* directed Rh(I)-addition to the proximal *bond **a** of* **88** (*i.e.* generation of rhodacyclobutane **I**), followed by β-hydride elimination and C–H reductive elimination. Conversely, treatment of aminocyclopropane **87** with a neutral Rh(I)-catalyst proceeded to form branched alkene **89** in 9% yield, *via* Rh(I)-addition to the distal *bond **b*** of **87** (Scheme

25A). It was postulated that the neutral Rh(I)-catalyst is not sufficiently Lewis acidic to be directed under non-carbonylative conditions. In the absence of the directing group, both cationic and neutral Rh(I)-sources inserted into the less hindered C–C bond (*bond **b***) of cyclopropane **90** to provide branched alkenes **91**/**92** (Scheme 25B). Taken together, these results confirm that carbamate-directed oxidative addition is possible if the Rh(I)-catalyst is sufficiently Lewis acidic.

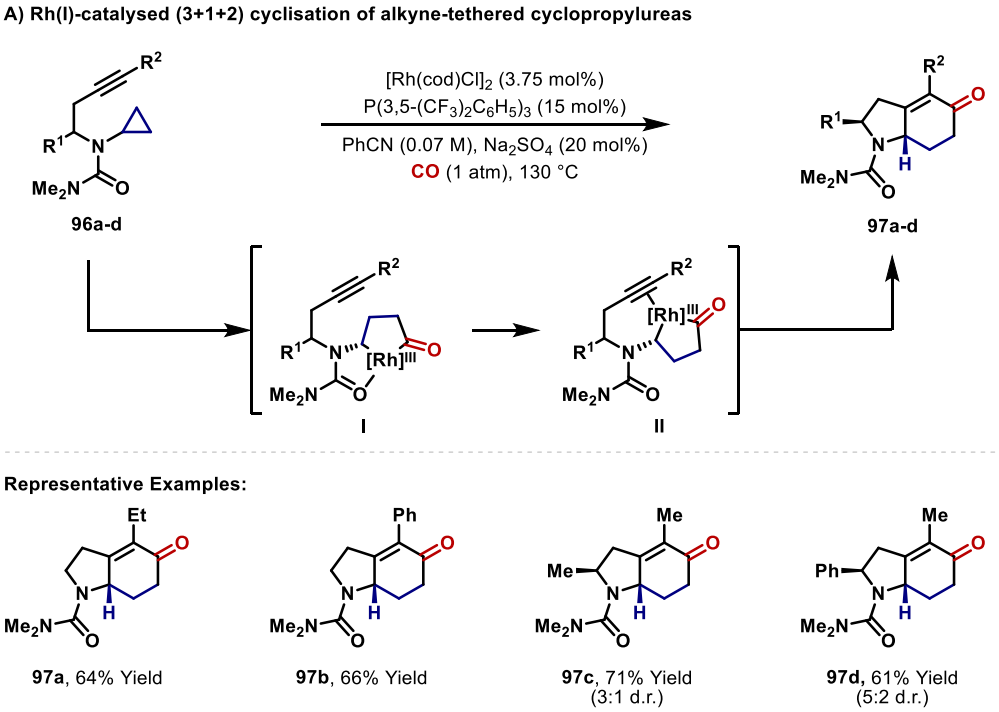


Scheme 25: Preliminary insertion experiments and evaluation of potential directing groups.

Next, to probe the relative properties of different carbamate-protecting groups, exposure of aminocyclopropanes **94a–c** to stoichiometric amounts of $[Rh(CO)_2Cl]_2$ resulted in the formation of dimeric rhodacyclopentanones **95a–c** (Scheme 25C).[15,18] The structures of rhodacyclopentanones **95a–c** were confirmed by X-ray diffraction. These experiments confirmed that rhodacyclopentanone formation results from directed Rh(I)-addition to the proximal cyclopropyl C–C bond and that the Rh–carbonyl directing group interaction remains ligated. Furthermore, the stretching frequency of the CO ligand *trans* to the directing group was used to quantify the donor strength of each directing group (Scheme 25C). From these experiments, the CO stretching frequencies indicate that directing group strength is proportional to the Lewis basicity of the carbonyl, and the following rank was determined: urea > carbamate > amide. The data acquired from these investigations was used to guide and inform subsequent methodology development.

1.3.1 Rh(I)-catalysed (3+1+2) cyclisation of cyclopropane derivatives

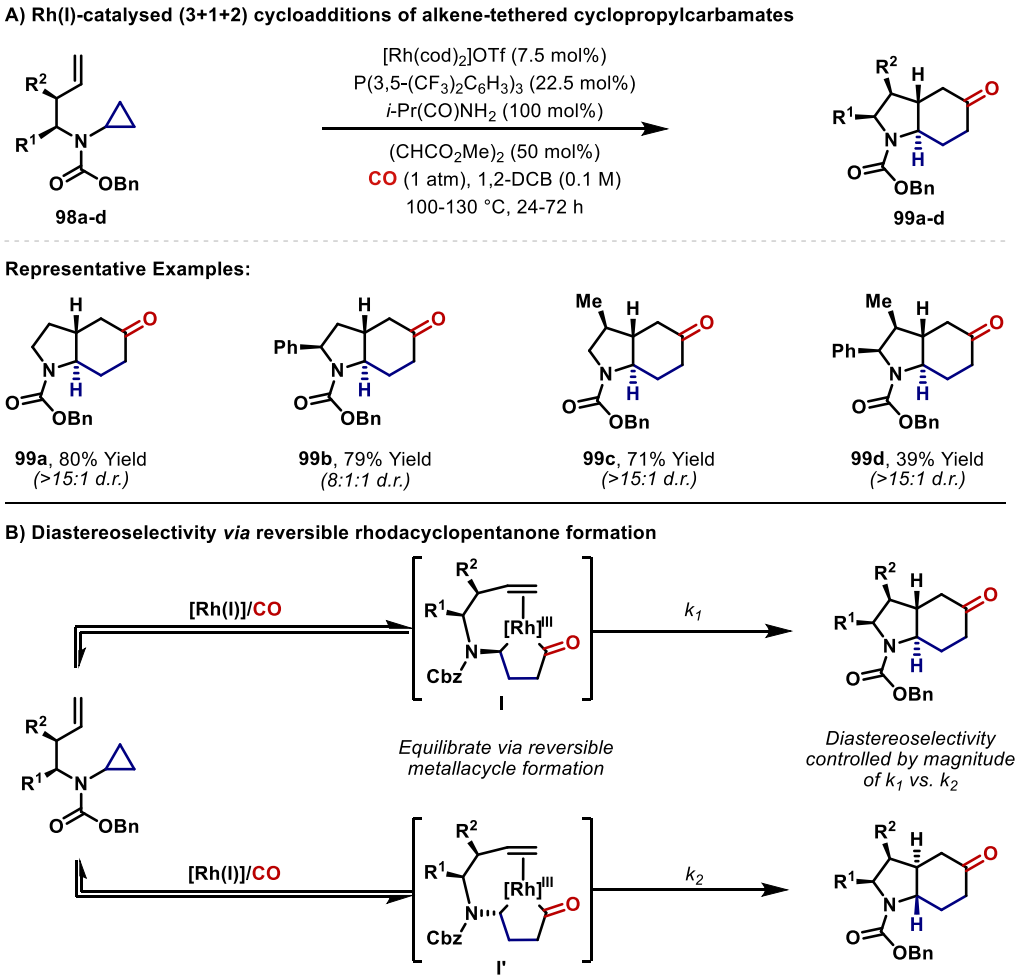
Having successfully demonstrated the selective generation of rhodacyclopentanones, subsequent studies investigated how this directing group strategy could be incorporated into a prototypical cycloaddition reaction. Initial studies focused on the development of a (3+1+2) cycloaddition between aminocyclopropanes, CO and tethered alkynes (Scheme 26). For such a transformation, the choice of *N*-directing group was critical as it must be sufficiently Lewis basic to outcompete the alkyne for coordination of the Rh(I)-catalyst prior to oxidative addition, but be labile enough to dissociate to allow alkyne coordination to the metal centre. It was discovered that strongly Lewis basic ureas fulfilled these criteria and offered enhanced efficiencies compared to carbamates and amides (*cf.* Scheme 25C).[15] Under optimised conditions, the process tolerated a range of substituents on the alkyne component, including alkyl- and aryl- substituted variants **96a**–**b**, which afforded the desired cycloadducts **97a**–**b** in 64% and 66% yield respectively. Additionally, for substrates possessing substituents on the tether (*e.g* **96c** and **96d**) good yields were obtained (*e.g.* 71% yield for **97c** and 61% for **97d**) with moderate levels of diastereoselectivity.



Scheme 26: Development of a prototype Rh(I)-catalysed carbonylative cyclisation of aminocyclopropanes.

In 2015, the Bower group published a second (3+1+2) cycloaddition involving Cbz-substituted aminocyclopropanes **98a–d**, CO and a tethered alkene unit to afford bicyclic ketones **99a–d** in moderate to excellent yield, and with high selectivity for a *trans*-ring junction (Scheme 27).[17] In this example, it was found that a less Lewis basic and more synthetically flexible carbamate could be used as the directing group. Notably, the high diastereoselectivities observed for R^1/R^2 substituted adducts (*e.g.*

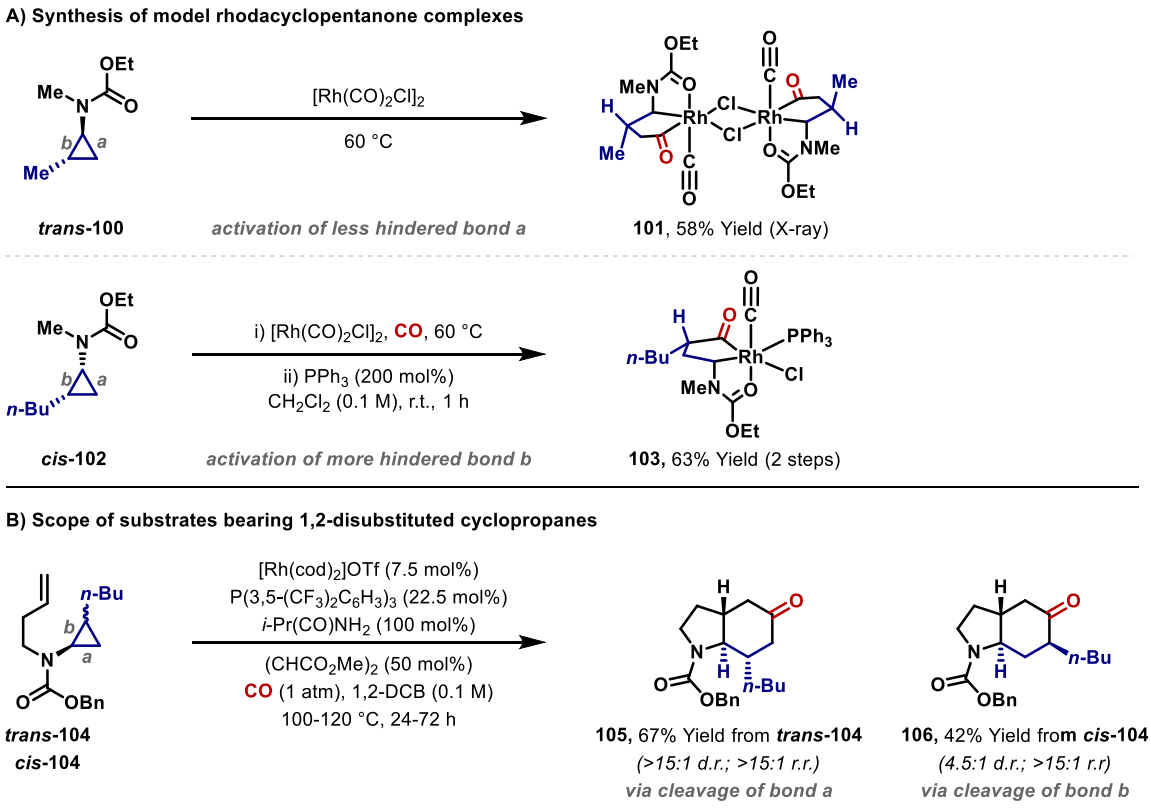
99b–**d**) likely arise *via* reversible formation of diastereomeric rhodacyclopetnaones **I** and **I'** under cationic conditions (Scheme 27B). In this way, diastereoselectivity is controlled by the relative ease of alkene insertion into either diastereomeric rhodacyclopentanones **I** and **II'**. This hypothesis was supported by exchange studies involving stoichiometrically generated rhodacyclopentanones. Additionally, optimisation studies revealed that the reaction rate and yield were greatly enhanced by the inclusion of (*E*)-$(CHCOOMe)_2$ and *iso*-butyramide additives. Whilst, the precise role of these additives was unclear, it was proposed that (*E*)-$(CHCOOMe)_2$ might act as an electron-deficient ligand.[95]



Scheme 27: Rh(I)-catalysed (3+1+2) cycloadditions of alkene-tethered cyclopropylcarbamates.

The processes described so far employed non-substituted aminocyclopropane units; however, further studies in the Bower group have demonstrated that more highly substituted systems are also effective. For such systems, an additional layer of complexity arises regarding the regioselectivity of C–C oxidative addition. Accordingly, to gain insight into the preferred regiochemical outcome of processes involving *trans*- and *cis*-1,2-disubstitued cyclopropanes, a series of model rhodacyclopentanones were prepared (Scheme 28A). It was discovered that exposure of *trans*-1,2-disubsubstitued aminocyclopropane ***trans*-100** to stoichiometric amounts of $[Rh(CO)_2Cl]_2$ led to

exclusive formation of dimeric species **101**. Rhodacyclopentanone **101** derives from regioselective cleavage of the less hindered proximal C–C bond (*bond* ***a***) of cyclopropane ***trans*-100**. On the other hand, *cis*-1,2-disubstituted aminocyclopropane ***cis*-102** underwent C–C bond activation at the more hindered proximal C–C bond (*bond* ***b***) to deliver species **103**. It was reasoned that for *cis*-1,2-disubstituted aminocyclopropanes, activation of the more electron-rich proximal bond (and therefore more strongly coordinating) is preferred as the steric constraints of the system are somewhat alleviated. The observations made in these studies correlated with the regioselectivities observed in (3+1+2) cycloaddition processes (Scheme 28B). For example, under optimised conditions, ***trans*-104** reacted *via* Rh(I)-addition to the less-hindered *bond* ***a*** to afford cycloadduct **105** in 67% yield with high levels of regiocontrol (15:1 r.r.). Conversely, ***cis*-104** reacted *via* Rh(I)-addition to the more-hindered *bond* ***b*** to provide cycloadduct **106** in 42% yield (15:1 r.r.). Therefore, the relative stereochemistry of the cyclopropane unit controls the regioselectivity of C–C bond activation; however, as shall be highlighted in subsequent studies, product regioselectivities do not always reflect the preferred regioselectivity of rhodacyclopentanone formation.

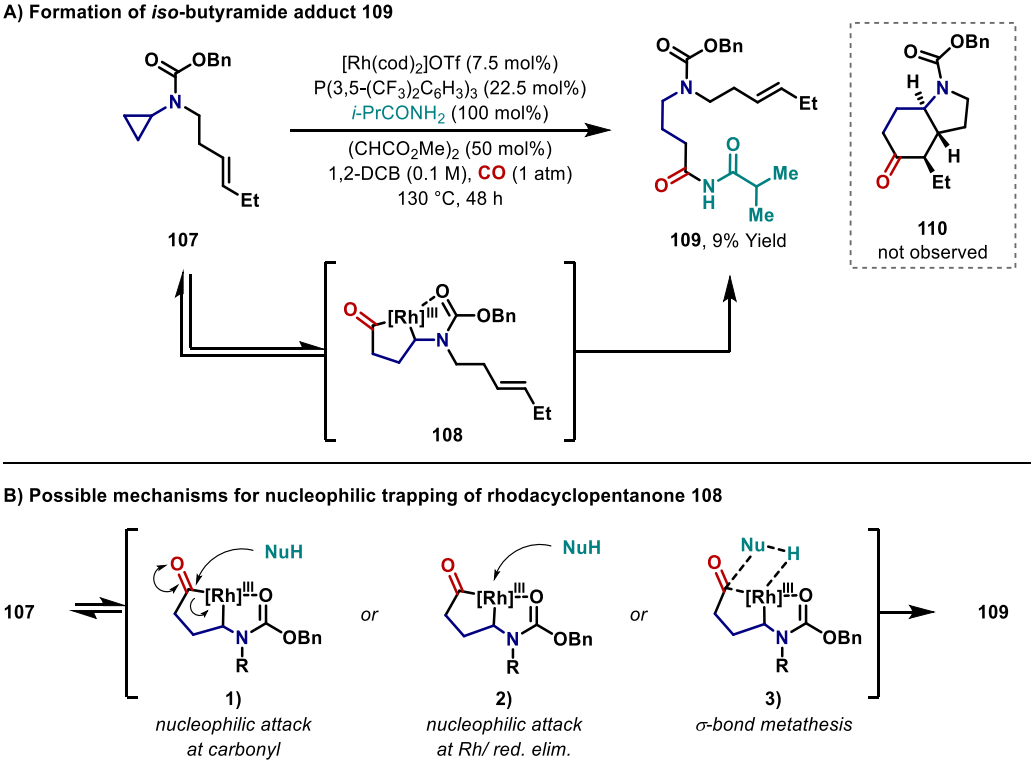


Scheme 28: Regioselectivity observed in the Rh(I)-catalysed cyclisation of 1,2-disubstituted cyclopropanes.

1.3.2 Nucleophilic addition to rhodacyclopentanones

1.3.2.1 Intermolecular nucleophilic addition to rhodacyclopentanones

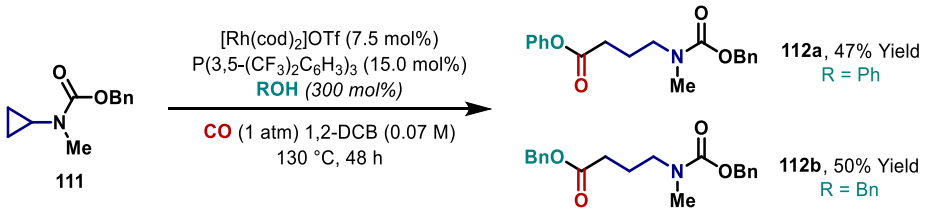
During investigations into the (3+1+2) cycloaddition of cyclopropylcarbamate **107**, former PhD student Dr. N. McCreanor observed the formation of carbonylation product **109** when *iso*-butyramide was used as a stoichiometric additive (instead of the desired cycloaddition product **110**), (Scheme 29A).[96] Althought the exact mechanism for the formation of imide **109** is unclear, it most likely involves initial formation of rhodacyclopentanone **108**, which is then intercepted by *iso*-butyramide by one of three mechanisms: (i) nucleophilic addition to the rhodacyclopentanone carbonyl; ii) nucleophilic addition to the Rh(III)-centre followed by C–N reductive elimination; or iii) σ-bond metathesis (Scheme 29B). In 2000, Murakami and co-workers demonstrated that rhodacyclopentanones can be trapped by *intramolecular* phenolic oxygen nucleophiles.[97] In contrast to these processes, this result represents the first example of *intermolecular* nucleophilic addition to rhodacyclopentanones, and thus presented the opportunity to explore new modes of reactivity of rhodacyclopentanone-based catalysis.



Scheme 29: Formation of *iso*-butyramide adduct **109** and the possible modes of nucleophilic trapping of rhodacyclopentanone **108**.

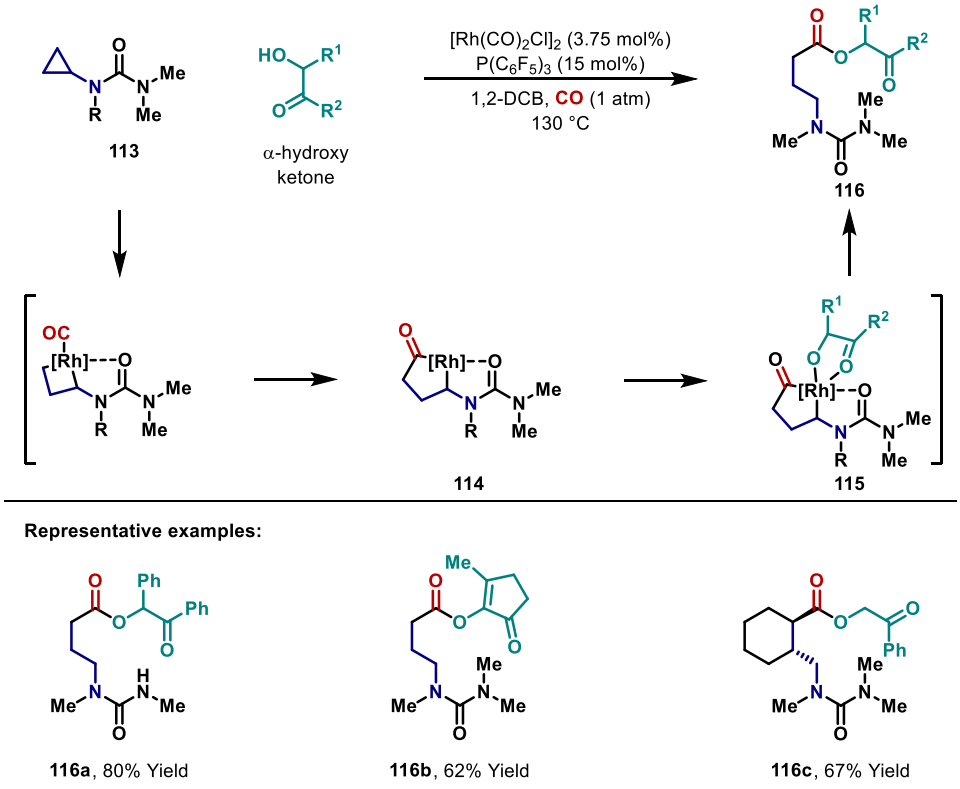
Intrigued by the unexpected formation of **109**, subsequent studies examined the nucleophilic addition of *O*-nucleophiles to cyclopropylcarbamate **111** (Scheme 30). Under partially optimised cationic conditions, phenol and benzyl alcohol were identified as effective nucleophiles, which afforded γ-amino-acid ester derivatives **112a** and **112b** in 47% and 50% yield, respectively. These investigations

were subsequently abandoned in favour of a more synthetically valuable *intramolecular* variant (see Section 1.3.2.2).



Scheme 30: Synthesis of γ-amino acid derivatives by intermolecular nucleophilic addition to rhodacyclopentanones.

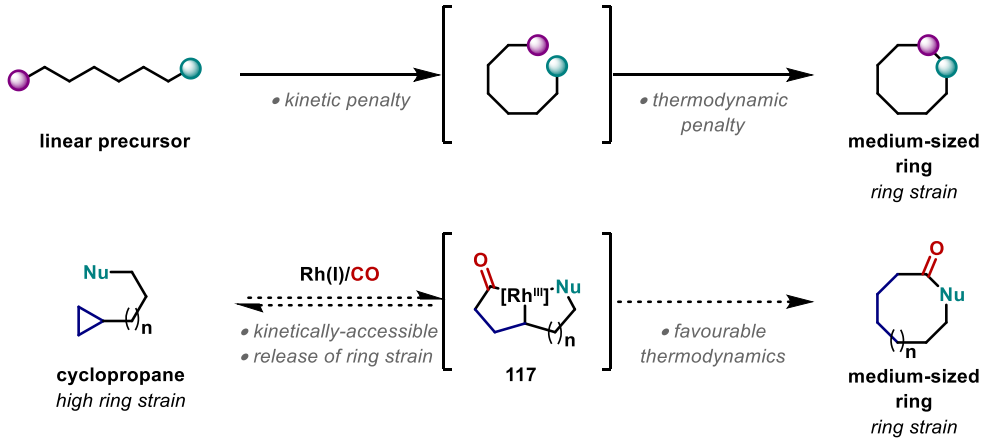
Recently, Wang and co-workers reported a related protocol involving intermolecular nucleophilic addition of α-hydroxy ketones to rhodacyclopentanones to generate α-amino acid esters (*e.g.* **116a**–**c**, Scheme 31).[98] This transformation presumably proceeds in an analogous manner (*cf.* Schemes 29 and 30) and involves initial formation of rhodacyclopentanone **114**. Next, a chelating nucleophile coordinates to rhodacyclopentanone **114**, generating metallacycle **115**, from which subsequent reductive elimination and protodemetallation affords the observed products **116a–c**.



Scheme 31: Wang's intermolecular nucleophilic addition of α-hydroxyketones to rhodacyclopentanones.

1.3.2.2 Intramolecular nucleophilic addition to rhodacyclopentanones

The discovery that rhodacyclopentanones could be trapped with intermolecular nucleophiles raised perhaps an even more interesting question: could rhodacyclopentanones be trapped with *intramolecular* nucleophiles to target valuable medium-sized heterocycles? It is well known that the synthesis of medium rings (8–11 membered) is challenging.[99-101] For example, classical cyclisation of linear chains to deliver medium rings is kinetically and thermodynamically unfavourable due to entropic and enthalpic effects (*vs.* 5–7 membered rings) (Scheme 32). Entropic effects concern the frequency of encounters between reactive groups at the chain ends of linear precursors. On the other hand, enthalpic effects are associated with the cyclised product and arise due to unfavourable interactions between atoms across the ring. As a result, the efficiency of end-to-end cyclisation-based approaches tends to be highly variable and substrate dependent. With regards to the synthesis of medium-sized rings *via* intramolecular nucleophilic addition to rhodacyclopentanones, it was hypothesised that the barrier to cyclisation could be alleviated by two means (Scheme 32). Firstly, the kinetic barrier to cyclisation would be reduced through the initial formation of a "normal-sized" *and* kinetically accessible bicyclic intermediate **117**. And secondly, the thermodynamic cost of forming a medium-sized ring product would be compensated by the release of cyclopropane ring strain.

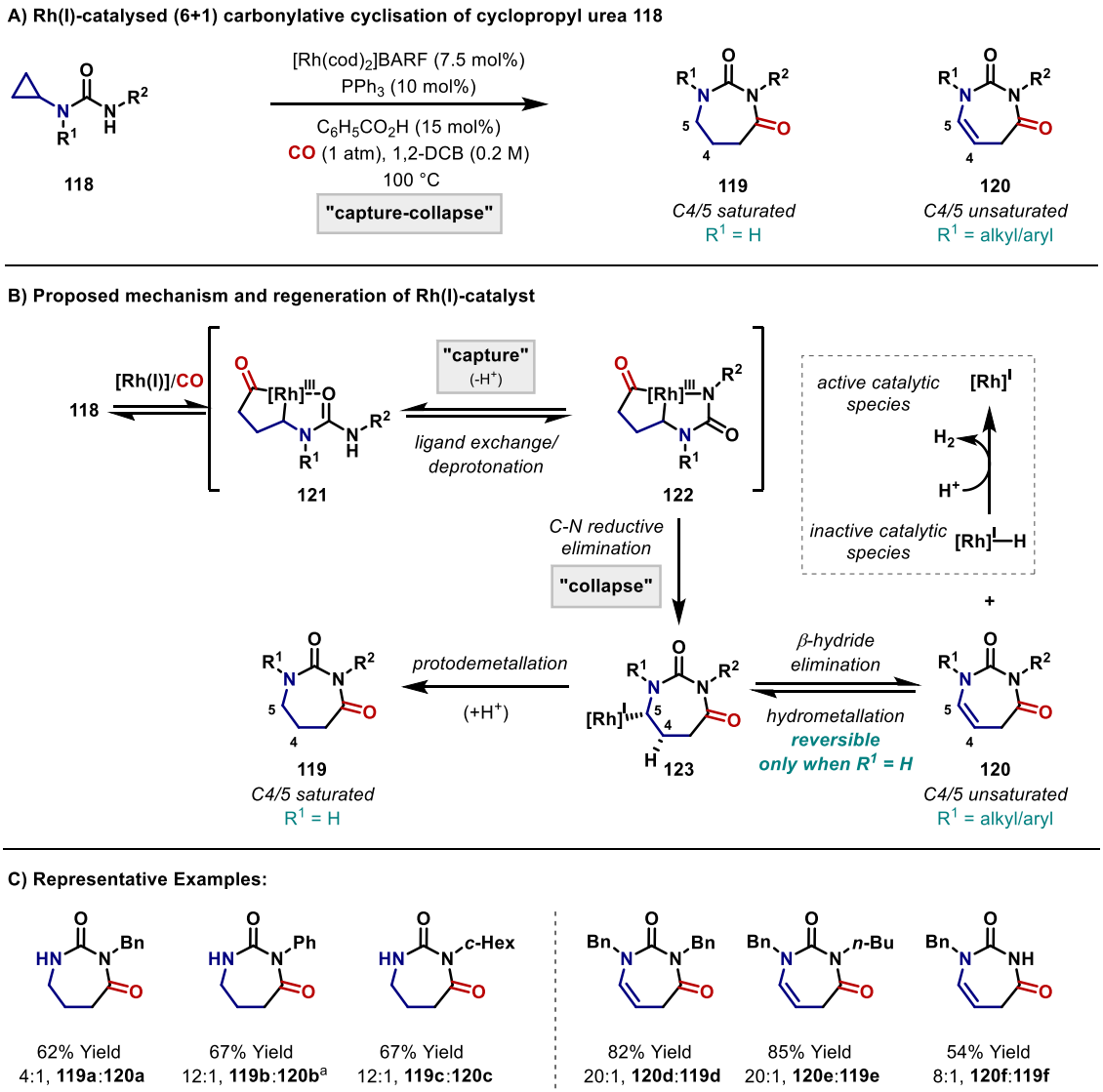


Scheme 32: Design strategy for the synthesis of medium-sized rings *via* kinetically accessible intermediate **117**.

1.3.2.3 (6+1) carbonylative cyclisation of cyclopropylureas

In order to examine the strategy proposed in Scheme 32, N. McCreanor and former PhD student Dr. S. Stanton synthesised a diverse library of aminocyclopropanes bearing carbonyl directing groups with tethered *O*- or *N*-nucleophiles and subjected them to carbonylative conditions (more details are provided in Chapter 3).[96,102] From these investigations, a prototype reaction was identified and developed in which cyclopropylurea substrates **118** underwent Rh(I)-catalysed carbonylative (6+1) cyclisation to form 7-membered diazepanes **119** and **120** (Scheme 33). In this transformation, rhodacyclopentanone **121** derived from cyclopropylurea **118** is "captured" by the pendent NH unit to form metallabicycle **122**

(Scheme 33B). At this stage, C–N reductive elimination ("collapse") affords Rh(I)-intermediate **123**, which then undergoes protodemetallation to diazepane **119**, or β-hydride elimination to diazepane **120**. β-Hydride elimination from intermediate **123** forms a Rh(I)-hydride species and it is speculated that the active Rh(I)-catalyst is regenerated by oxidative protonation and reductive elimination of dihydrogen.[97,103]

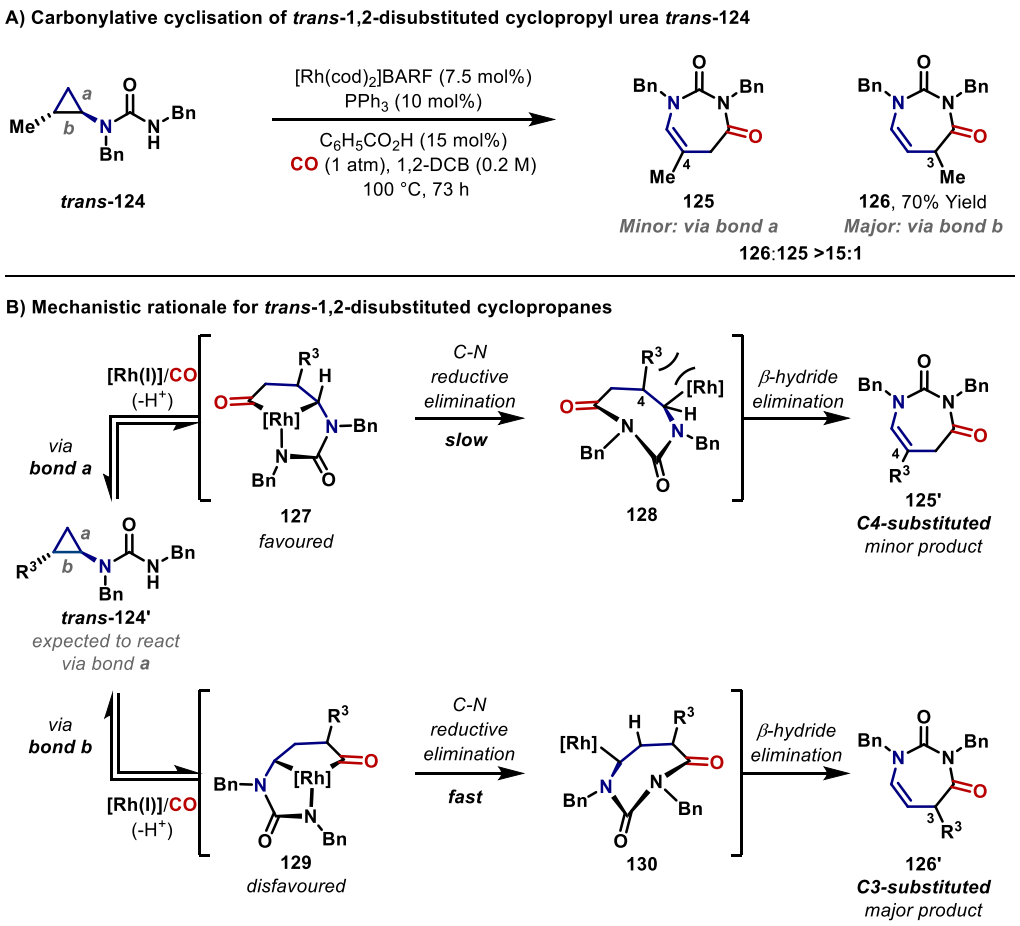


Scheme 33: "Capture-collapse" carbonylative heterocyclisation of cyclopropylureas to deliver 7-membered diazepanes.

Interestingly, it was discovered that the oxidation level at the C4/C5 position in the product can be controlled by the choice of R^1 substituent on the urea substrate, thereby allowing selective formation of either C4/C5 unsaturated or saturated products. More specifically, if R^1 is large (*i.e.* R^1 = alkyl or aryl), *irreversible* β-hydride elimination favours the unsaturated product **120**. Conversely, if R^1 is small (*i.e.* R^1 = H) *reversible* β-hydride elimination is operational, allowing for eventual protodemetallation to saturated product **119**. Under optimised carbonylative reaction conditions ($[Rh(cod)_2]BARF$, PPh_3,

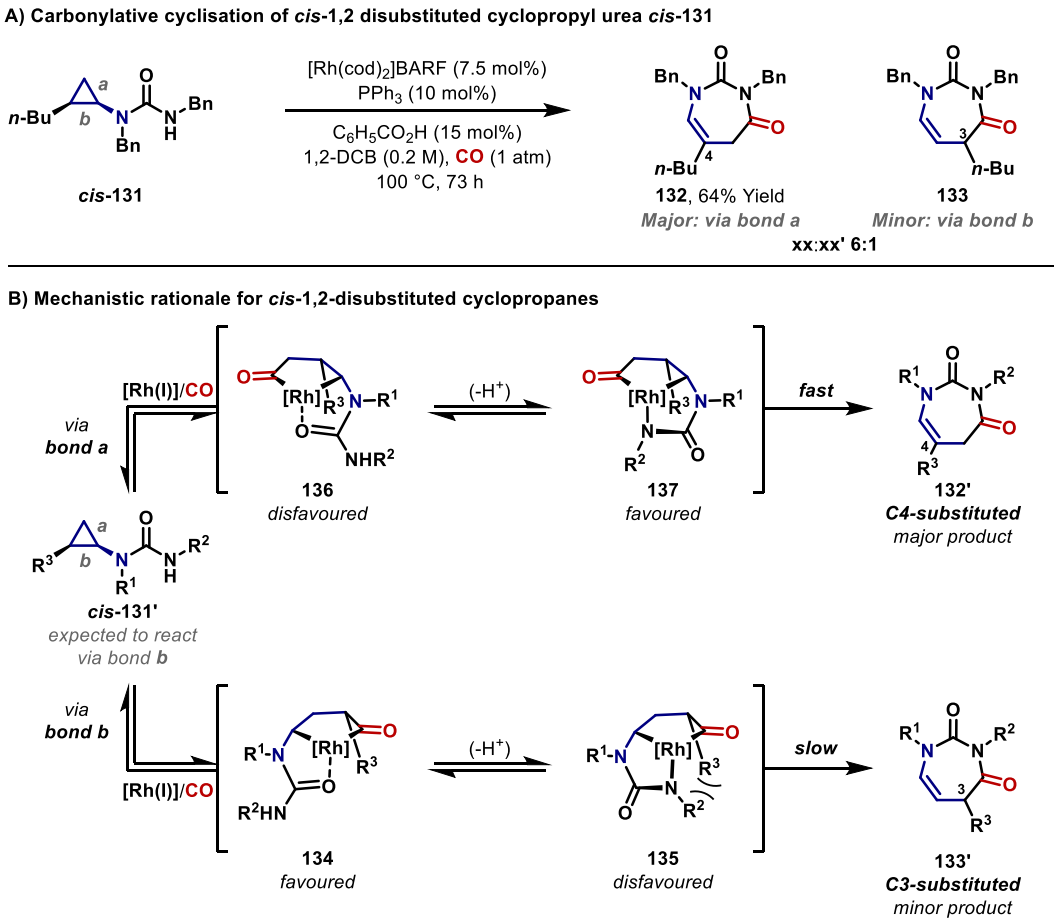
$C_6H_5CO_2H$, 1,2-DCB, 100 °C), a range of *N*,*N*'-disubstituted cyclopropylureas **118a**–**c** and trisubstituted cyclopropylureas **118d**–**f** underwent cyclisation to the corresponding diazepane products in 54–85% yield (Scheme 33C). The substrates for this process are easily accessible by reacting the corresponding aminocyclopropanes with the desired *N*-aryl or *N*-alkyl isocyanate which, in turn, allows the two-step synthesis of a variety of interesting and challenging heterocyclic ring systems.

Processes involving *trans*- and *cis*-1,2-disubstituted cyclopropane systems led to unexpected regiochemical outcomes and provided important insights into the mechanism (Schemes 34 and 35). For example, carbonylative cyclisation of *trans*-1,2-disubstituted cyclopropylurea ***trans*-124** afforded C3-substituted diazepane **126** as the major product, where C–C bond activation has occurred *via* the more hindered *bond* ***b*** (Scheme 34). *The selectivity observed is the inverse to that discussed previously in Section 1.3.1* (*cf*. Scheme 28). This unanticipated reactivity was rationalised by invoking C–N reductive elimination as the first irreversible step of the process (Scheme 34B). While C–C bond activation of *bond* ***a*** is more sterically accessible, subsequent C–N reductive elimination of **127** to metallacycle **128** is likely to be slow due to the developing steric clash between the bulky Rh(III)-centre and the R^3-substituent. Consequently, under equilibrating conditions, re-protonation of the nitrogen, retrocarbonylation and C–C reductive elimination regenerates cyclopropylurea ***trans*-124'**. From here, reversible metallacycle formation enables access to the less favourable rhodacyclopentanone **129** (*via* Rh(I)-addition to the more hindered *bond* ***b*** of ***trans*-124'**), which then undergoes more facile C–N reductive elimination to metallacycle **130** (*cf*. **128**, 1,2- *vs.* 1,3-relationship) and after β-hydride elimination, product **126'** is obtained.



Scheme 34: Regioselectivity of the (6+1) carbonylative cyclisation of *trans*-1,2-disubstituted cyclopropylureas.

On the other hand, carbonylative cyclisation of *cis*-1,2-disubstituted cyclopropylurea ***cis*-131** delivered C4-substituted diazepane **132** as the major product (Scheme 35A), whereby C–C bond activation occurred *via* the less hindered *bond **a***. *The selectivity observed is the inverse to that discussed previously in Section 1.3.1* (*cf.* Scheme 28). The observed switch in regiochemical outcome was justified by a similar selectivity model (Scheme 35B). In this instance, rhodacyclopentanone formation *via bond **b*** is favoured leading to metallacycle **134**; however, subsequent C–N reductive elimination (**134** to **135**) is proposed to be slow due to developing steric clashes between the N-R^2 group and the R^3-substituent. As a result, reversible rhodacyclopentanone formation allows access to alternative metallacycle **136**, from which C–N reductive elimination is more facile and this effect leads to selective formation of C4-substituted diazepane **132'**. Taken together, the results for *trans*- and *cis*-1,2-disubstituted cyclopropane systems indicated that regioselectivity is determined by the ease of C–N reductive elimination and not by the ease of C–C activation.

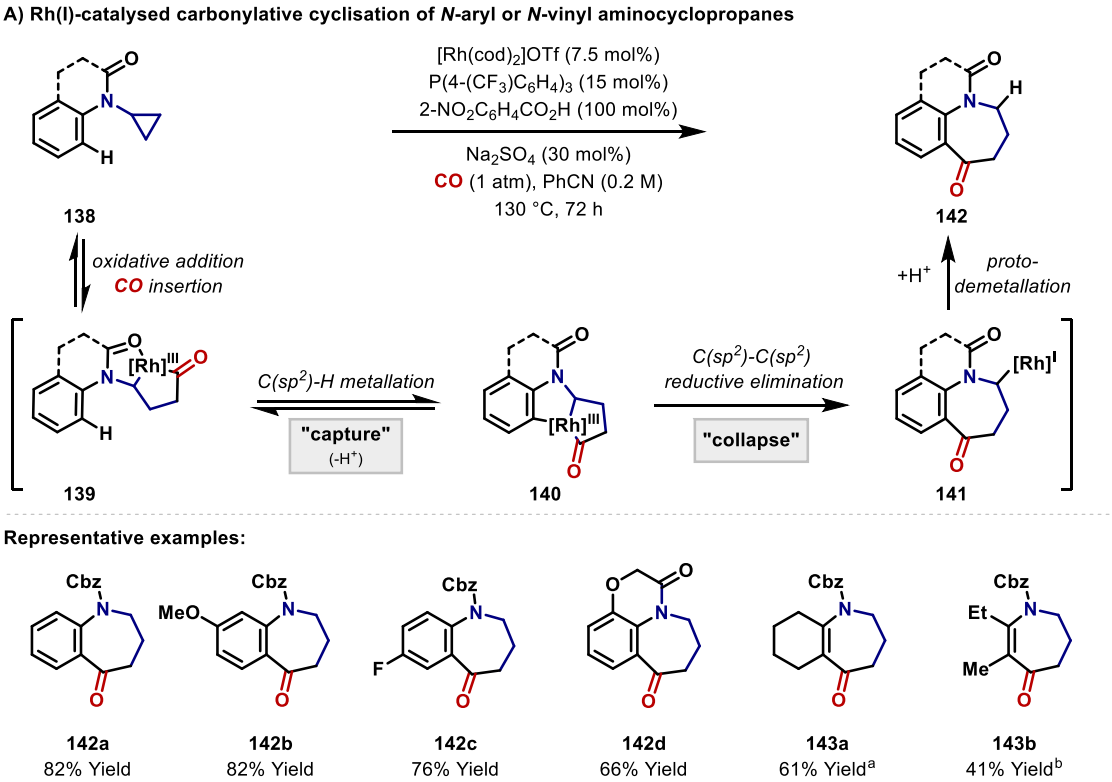


Scheme 35: Regioselectivity of the (6+1) carbonylative cyclisation of *cis*-1,2-disubstituted cyclopropylureas.

1.3.2.4 (6+1) carbonylative cyclisation of *N*-aryl and *N*-vinyl aminocyclopropanes

Building upon the above successes, the Bower group further explored the power of "capture-collapse" heterocyclisations and, in 2018, disclosed the first example that involved C-based nucleophiles.[21] Under an atmosphere of CO, Rh(I)-catalysed cyclisation of *N*-aryl aminocyclopropanes **138** generated 7-membered benzazepines **142** (Scheme 36).[104] Here, the mechanistic pathway was proposed to proceed *via* carbonyl directed C–C bond activation of aminocyclopropane **138** to rhodacyclopentanone **139**, followed by C–H metallation ("capture") to give 5,5-metallabicyclic intermediate **140**. Subsequent C(sp^2)–C(sp^2) reductive elimination ("collapse") to **141** and protodemetallation affords the target azepines **142**. This study demonstrated for the first time the compatibility of combining C(sp^2)–H metallation step from rhodacyclopentanones with C–C bond forming reductive elimination to form azepines. Under optimised conditions ([Rh(cod)$_2$]OTf (7.5 mol%), P(4-$CF_3C_6H_4$)$_3$ (15 mol%), 2-$NO_2C_6H_4CO_2H$ (100 mol%) in PhCN) benzazepine **142a** was generated in 82% yield. Notably, in the absence of 2-$NO_2C_6H_4CO_2H$, the yield of **142a** was less than 30%, thus suggesting that the acid additive aids the final protodemetallation step (**141** to **142**). The reaction proved tolerant of a range of electron-withdrawing and electron-donating substituents on the aryl ring. For systems with *meta*-substituents, the process was highly regioselective, as demonstrated by the formation of benzazepine **142b** where

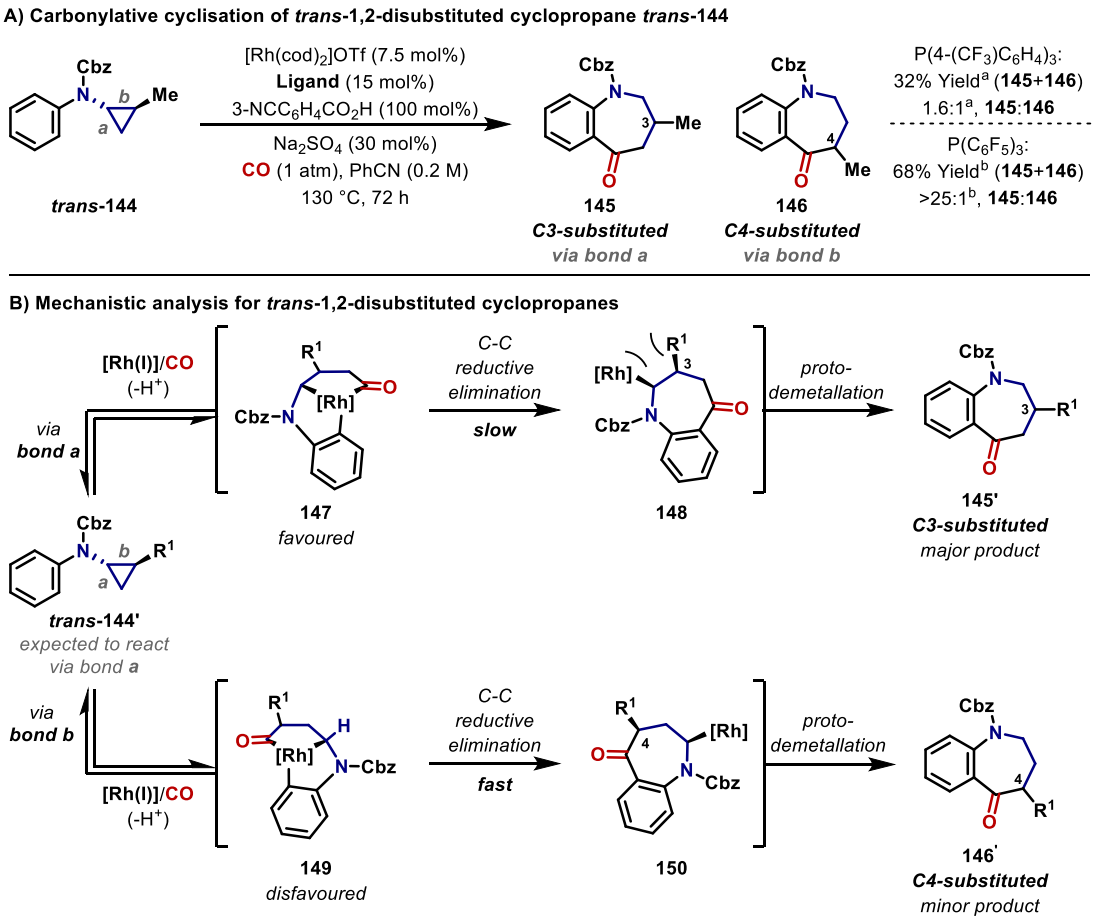
C–C bond formation has occurred at the more sterically accessible *ortho*-position. Importantly, the scope was further elaborated to include *N*-vinyl substrates, which allowed direct access to non-benzofused azepine products **143a**–**b** in 41–61% yield. A series of mechanistic studies on an *N*-aryl system suggest that C–C reductive elimination is the first irreversible step of the catalytic cycle.



Scheme 36: Synthesis of (benz)azepines from *N*-aryl or *N*-vinyl cyclopropanes by sequential C–C and C–H bond activation. [a] 2-$NO_2C_6H_4CO_2H$ was omitted. [b] 3-$NCC_6H_4CO_2H$ was used instead of 2-$NO_2C_6H_4CO_2H$.

Extension of the protocol to *trans*-1,2-disubstituted aminocyclopropanes proved challenging and required further optimisation. Using the same conditions as shown in Scheme 36, *trans*-1,2-disubstituted aminocyclopropane ***trans*-144** underwent Rh(I)-catalysed cyclisation to form approximately equal ratios of C3- and C4-methylated regioisomers **145** and **146** (Scheme 37). By a similar hypothesis to that presented in Section 1.3.2.3, the former product arises from the kinetically favoured rhodacyclopentanone **147**, but subsequent C–C reductive elimination is presumed to be slow due to the developing steric clash between the Rh(III)-centre and the C3 substituent (Scheme 37B). Accordingly, reversible metallacycle formation provides kinetically disfavoured regioisomer **149**, which can undergo C–C reductive elimination more readily to give C4-substituted product **146**. To circumvent this issue, a more electron-deficient phosphine ligand was selected as this might promote faster C–C reductive of **147** to **148**.[105] Indeed, replacement of P(4-$CF_3C_6H_4$)$_3$ with P(C_6F_5)$_3$ enabled selective formation of the C3-regioisomer **145** in 68% yield. Substituted cyclopropanes are easily

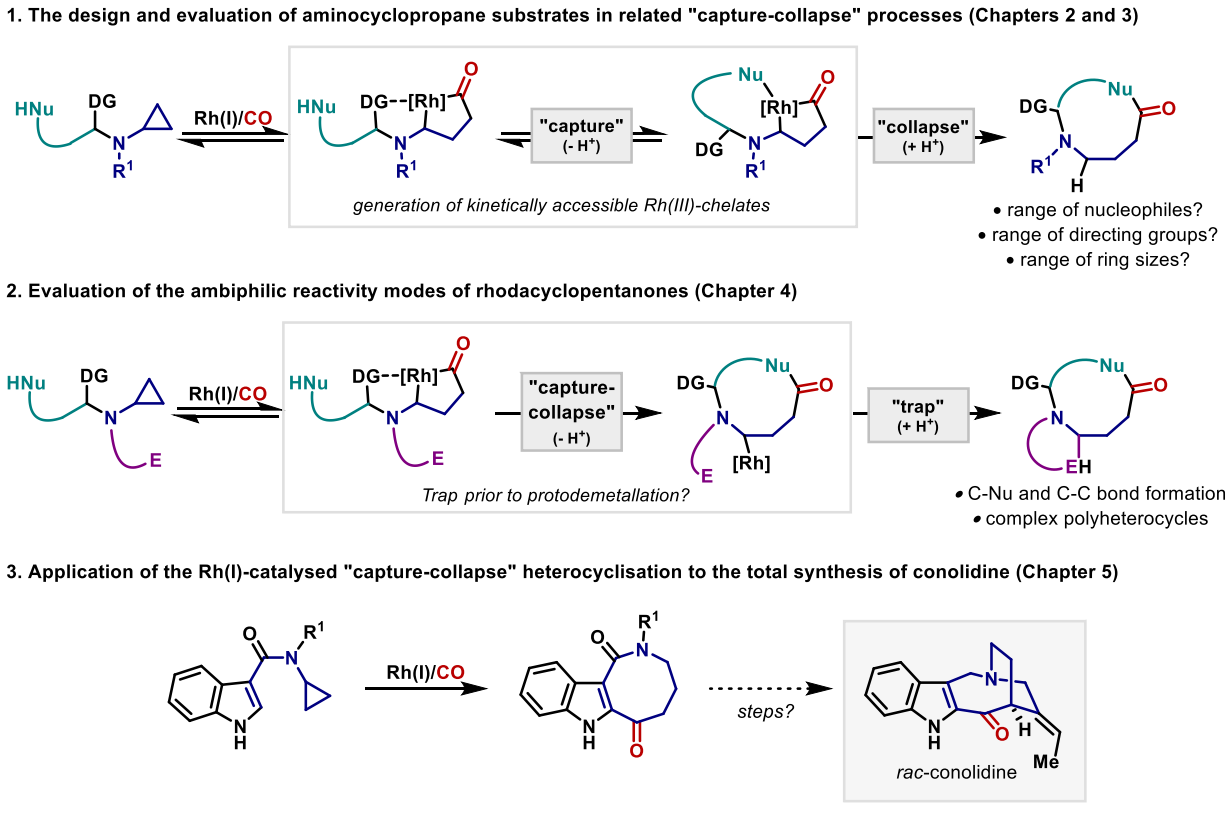
accessed in enantioenriched form and pleasingly, these new conditions enabled stereospecific introduction of substituents at the C3 position.



Scheme 37: Rh(I)-catalysed carbonylative cyclisation of *trans*-1,2-disubstituted cyclopropanes. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [b] Isolated yield.

1.4 Project Aims

As outlined in the previous section, the Bower group has a long-standing interest in the C–C bond activation of aminocyclopropanes to access sp^3-rich heterobicyclic molecules *via* reactive rhodacyclopentanone intermediates. One significant advancement of this work led to the discovery that rhodacyclopentanones could be trapped with pendant nucleophiles to form 7-membered *N*-heterocycles *via* the "capture-collapse" heterocyclisation strategy. Outside of these pioneering examples and π-insertion processes, the reactivity of rhodacyclopentanones remains relatively unexplored. However, intramolecular nucleophilic addition to rhodacyclopentanones is, in principal, well-suited for the synthesis of valuable medium-sized rings. Therefore, the primary goal of this project is to evaluate further the generality of the "capture-collapse" heterocyclisation protocol to form 7- and 8-membered heterocyclic products (Chapters 2 and 3). Subsequent investigations will examine the ambiphilic reactivity of rhodacyclopentanones in the synthesis of polyheterocycles (Chapter 4). Finally, application of the "capture-collapse" heterocyclisation methodology will be examined in the total synthesis of (*rac*)-conolidine (Chapter 5). Herein, the successful (and unsuccessful) realisation of these goals is discussed.



Scheme 38: Project Aims.

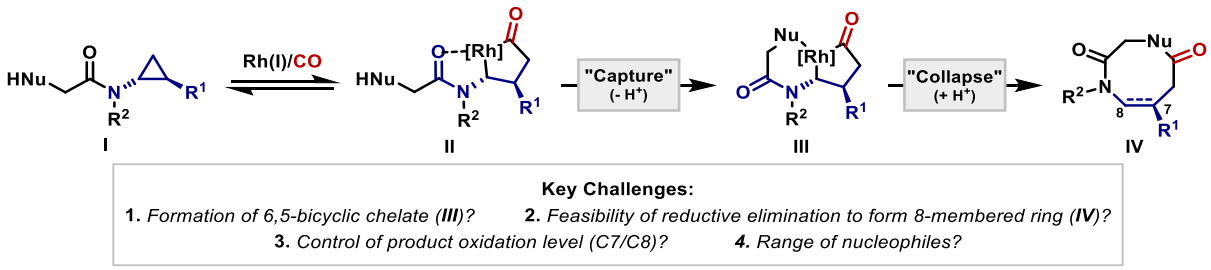
Chapter 2 – Modular access to 8-membered *N*-heterocycles by directed C–C bond activation of aminocyclopropanes

Parts of the work detailed in this chapter have been adapted from a publication by Boyd et al.

(*Angew. Chem. Int. Ed.* **2019**, *58*, 18844)

2.1 Reaction design and discovery

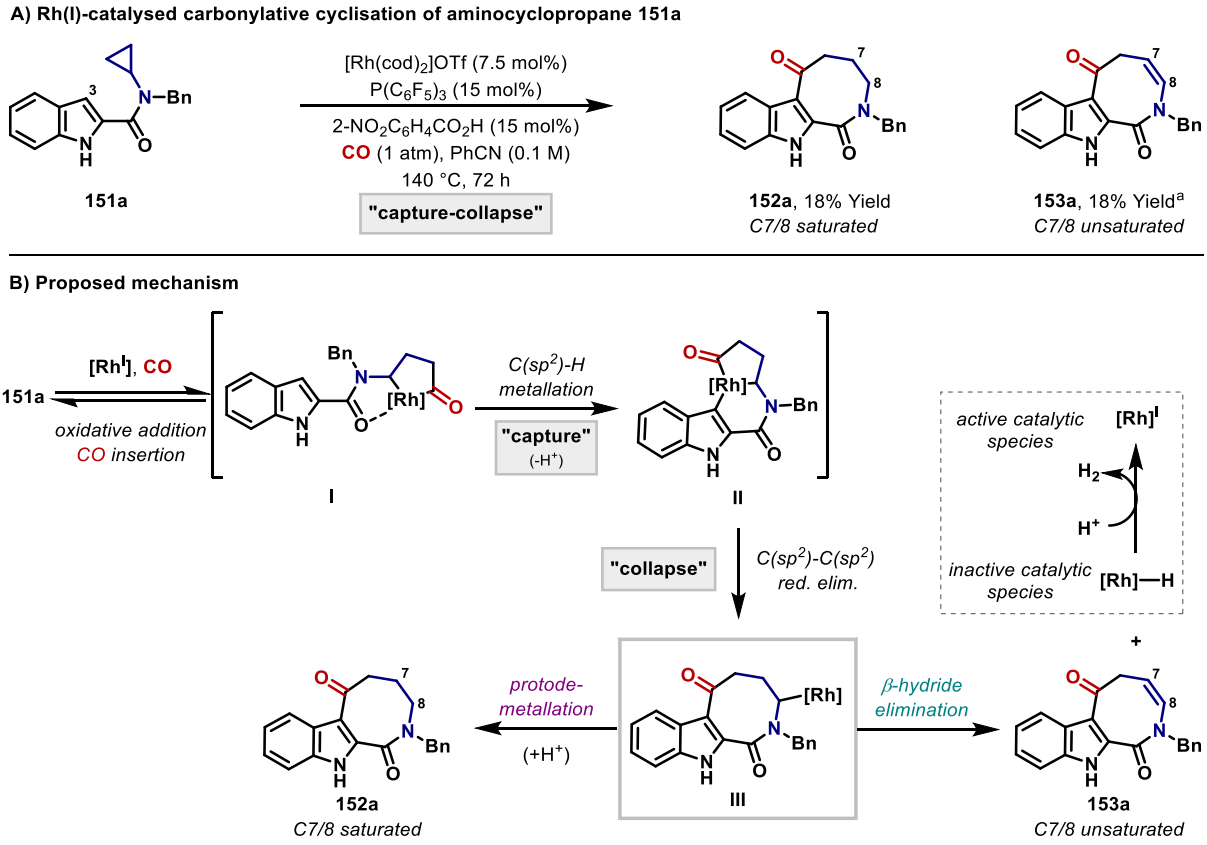
Following the successful development of a metallacycle-based blueprint to access 7-membered heterocycles, the question was raised as to whether related "capture-collapse" heterocyclisations could be employed to generate ≥8-membered heterocycles. With this definitive goal in mind, substrates of type **I** were designed and trialled under carbonylative cyclisation conditions. (Scheme 39). It was anticipated that nucleophilic "capture" of rhodacyclopentanone **II** (**II** to **III**) and subsequent C–C reductive elimination ("collapse") would furnish 8-membered *N*-heterocycles with the general structure **IV**. As stated previously, this approach is appealing because the release of cyclopropane ring strain and the intermediacy of kinetically accessible bicycles (*i.e.* **II** and **III**) avoid the usual enthalpic and entropic barriers associated with medium-sized ring closure. Additionally, it was reasoned that incorporation of the carbonyl directing group into the new ring system would impart a conformational bias (restricted rotation of the amide unit) and consequently enhance access to key intermediate **III**. However, the success of such a strategy is dependent on (1) equilibrium access to the 6,5-metallabicycle **III** and (2) the barrier for C-Nu reductive elimination (*i.e.* **III** to **IV**).



Scheme 39: Generalised reaction design for the synthesis of 8-membered *N*-heterocycles by "capture-collapse" heterocyclisation.

In order to validate the above hypothesis, aminocyclopropylamide **151a** was readily synthesised in two steps (*vide infra*) and exposed to carbonylative conditions using a cationic Rh(I)/PhCN catalyst system (Scheme 40). Under these conditions, amide **151a** underwent cyclisation to afford equal amounts of C7/8 *saturated* heterocycle **152a** and C7/8 *unsaturated* heterocycle **153a**. As shown in Scheme 40, the proposed mechanism proceeds *via* initial carbonyl directed formation of rhodacyclopentanone **I**. Next, directing group dissociation enables metallation of the indole unit by the Rh(III)-centre to form 6,5-metallabicyclic **II**. Subsequent C(sp^2)–C(sp^2) reductive elimination secures

the new C–C bond and generates Rh(I)-alkyl intermediate **III**. From here, either protodemetallation *or* competing β-hydride elimination pathways deliver heterocycles **152a**/**153a** respectively. Interestingly, heterocycle **152a** exhibited a broadened ^{1}H NMR spectrum at room temperature; variable temperature NMR studies suggest that this is due to slow conformational interconversion of the strained 8-membered ring (more details are provided in Section 7.3.1). Additionally, no competing C–N bond formation *via* the NH unit of **151a** was observed. Motivated by the novel structures of heterocycles **152a**/**153a** and given the therapeutic importance of medium ring heterocycles, indole **151a** was selected as a model substrate for further optimisation studies.



Scheme 40: Carbonylative ring expansion of aminocyclopropane **151a** delivered 8-membered *N*-heterocycles **152a** and **153a**. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

2.2 Biological importance of medium rings

Cyclic molecular scaffolds constitute a vital component of a myriad of biologically active natural products and medicinally important synthetic molecules.[106,107] For example, medium ring heterocycles have been incorporated into the design of antimalarial, anticancer, anticoagulant small molecules, as well as protein kinase D, protein-tyrosine phosphatase 1B and Rho kinase inhibitors (for selected examples see Figure 2).[108-113] Compared to normal ring sizes and macrocycles (12+ membered rings), the conformational constraints and diverse 3D spatial properties of medium-sized frameworks are often

associated with favourable pharmacological properties, such as; (i) increased binding affinity to a receptor,[114,115] (ii) improved bioavailability[115] and, in some cases, (iii) enhanced cell permeability.[116,117] However, despite these attractive features, medium rings are noticeably underrepresented in marketed drugs and drug discovery libraries. Arguably, the main obstacle preventing further application is the lack of broadly applicable methodologies available for accessing medium ring targets.[106,118-120] Indeed, cyclisation-based approaches and cycloaddition reactions to generate 5- and 6- membered rings are common, but similar strategies to form medium-sized rings are often inhibited by entropic factors and transannular interactions (see Scheme 32).

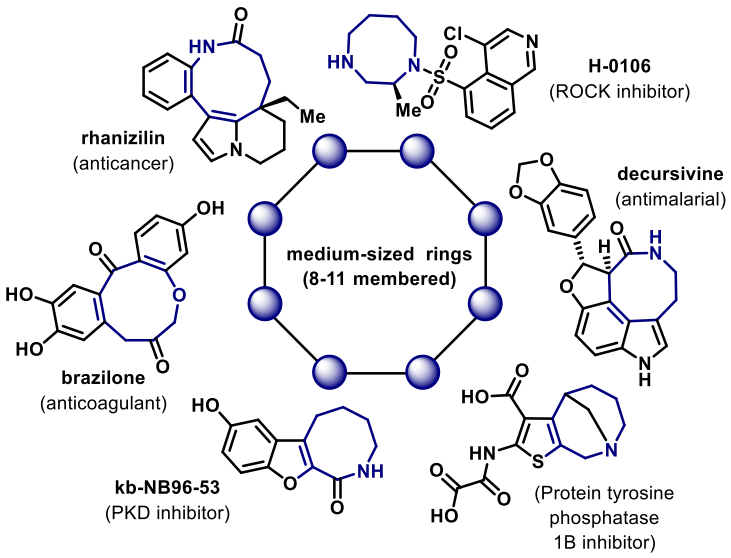
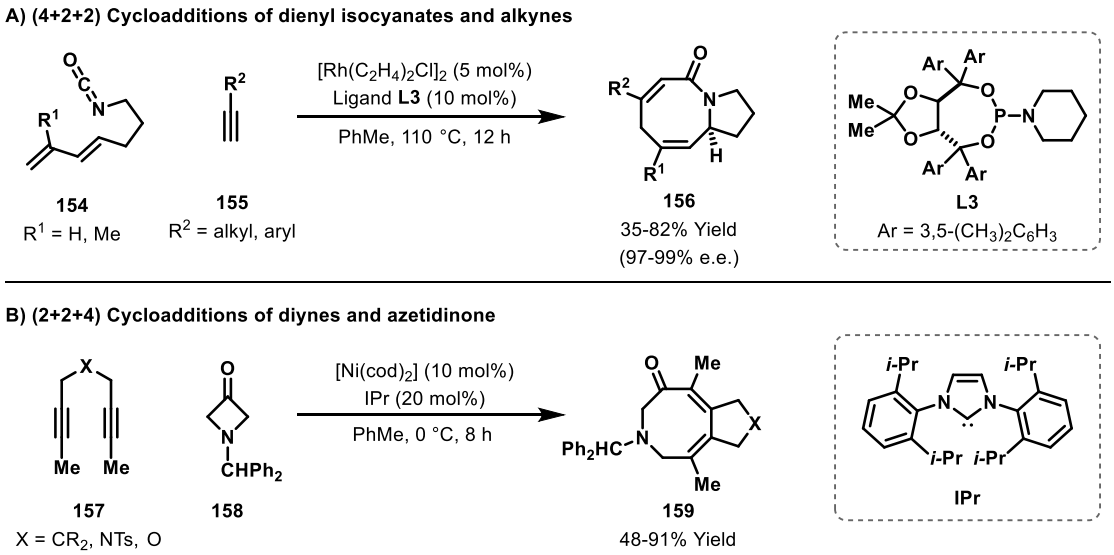


Figure 2: Bioactive medium-sized heterocycles.

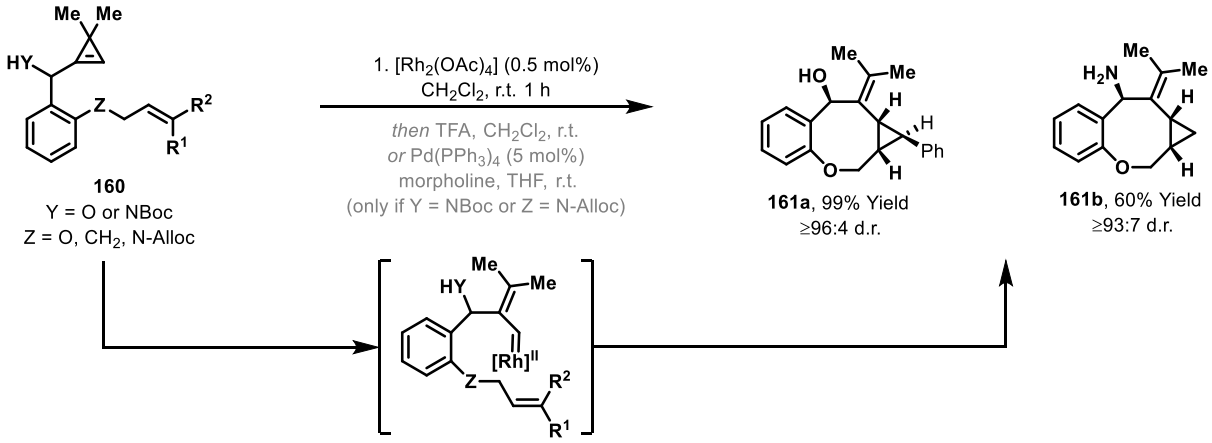
2.3 Synthetic approaches to 8-membered N-heterocycles

To address this issue, recent developments in metal-catalysed cycloadditions have significantly increased the number of approaches to 8-membered carbocycles.[121] Notable reports include metal-mediated (2+2+2+2),[122,123] (4+2+2),[124-126] (4+4)[127,128] and (6+2)[129-131] cycloadditions. Notwithstanding these advances, catalytic approaches that deliver *N*-heterocycles have been slow to emerge. The first documented Rh(I)-catalysed (4+2+2) cycloaddition for the enantioselective synthesis of *N*-heterocycles was reported by Rovis and co-workers in 2009 (Scheme 41A).[132] In this example, exposure of dienyl isocyanates **154** and terminal alkynes **155** to a neutral Rh(I)-catalyst, in combination with a chiral phosphoramidite ligand **L3**, afforded bicyclic azocines **156** in good yields and with excellent enantioselectivity. Following this publication, Louie and co-workers reported the synthesis of azocanes **159** through a Ni(0)-catalysed cycloaddition of diynes **157** and azetidinone **158** under mild conditions (Scheme 41B).[133]



Scheme 41: Transition metal-catalysed cycloadditions delivering 8-membered *N*-heterocycles.

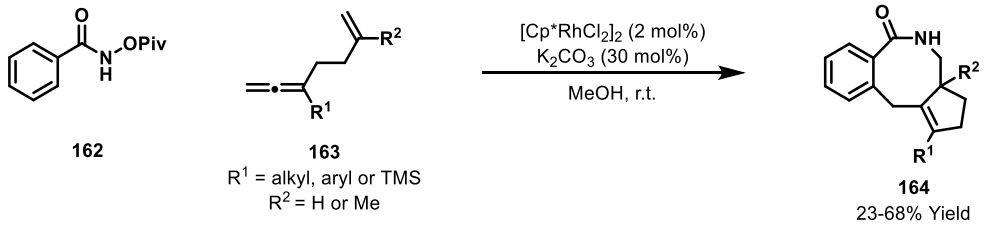
As shown above in Figure 2, benzannulated and heteroaromatic-annulated heterocycles form the structural core of numerous therapeutically important natural and synthetic molecules. To date, common synthetic routes to medium-sized benzannulated heterocycles include lactonisation/lactamisation,[120] transition metal-catalysed cross-couplings[134,135] and ring-closing metathesis.[136,137] Of particular relevance to this work, Cossy and co-workers reported the synthesis of benzoxocines (*e.g.* **161a** and **161b**) possessing a [6.1.0] bicyclic framework *via* Rh(II)-catalysed cycloisomerisation of cyclopropenes **160** (Scheme 42).[138] Under optimised conditions, benzoxocine **161a** was obtained in excellent yield and diastereoselectivity. The same strategy could be combined with a *N*-protecting group cleavage step to access benzazocane **161b**, albeit with reduced efficiency.



Scheme 42: Rh(II)-catalysed cycloisomerisation of cyclopropenes to generate benzoannulated 8-membered *N*-heterocycles.

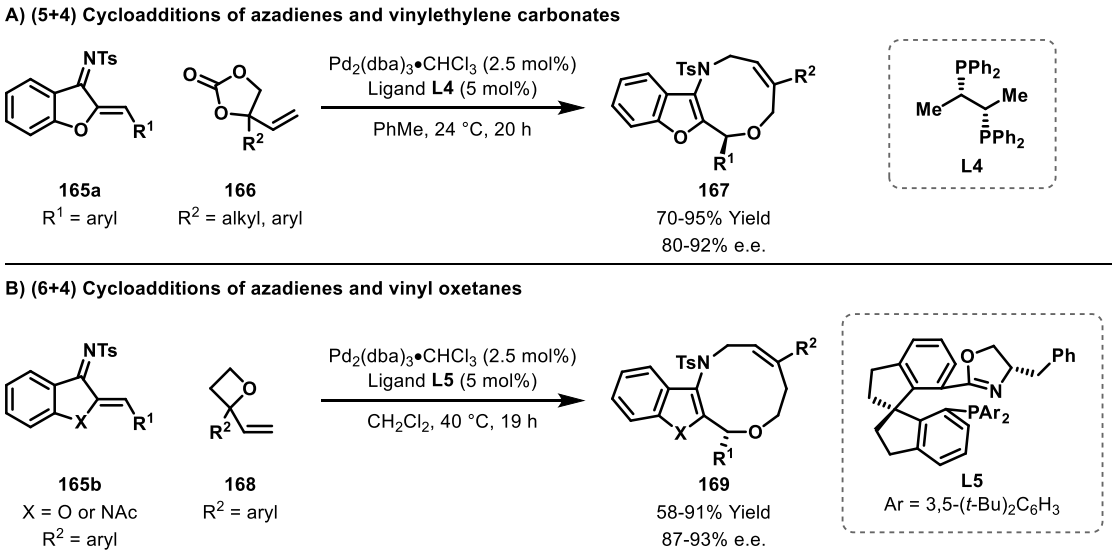
In 2015, Ma and co-workers developed a Rh(III)-catalysed (4+2+2) cyclisation between *N*-pivaloyloxy benzamides **162** and 1,6-allene-enes **163** to construct 8-membered lactams (Scheme

43).[139] These reactions proceeded at room temperature to afford the target benzannulated products **164** in moderate to good yield (23–68% yield).



Scheme 43: Rh(III)-catalysed (4+2+2) cycloadditions of benzamides and 1,6-allene-enes.

Although progress has been made to access benzannulated carbo- and heterocycles,[120] complementary methods that provide heteroarene-fused medium-sized rings remain scarce. In this regard, there are only limited examples using Au, Ag or Ir catalysis to afford indole-fused 8-membered heterocycles.[140-146] More recently, elegant examples by Zhao and co-workers have demonstrated the enantioselective synthesis of indole- or benzofuran-fused 9- and 10-membered heterocycles **167**/**169** by Pd(0)-catalysed (5+4)[147,148] or (6+4)[149] intermolecular cycloaddition reactions of azadienes (**165a** or **165b**) with vinylethylene carbonates **166** or vinyl oxetanes **168** (Scheme 44).



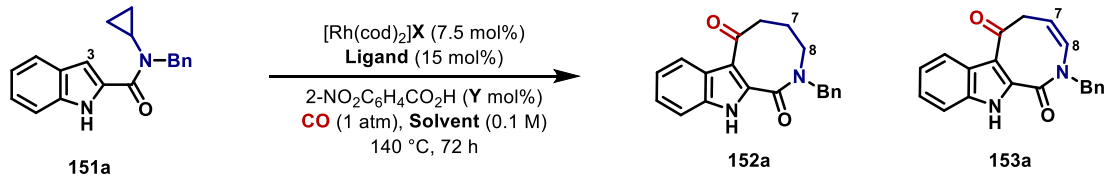
Scheme 44: Pd-catalysed cycloadditions delivering indole- or benzofuran-fused 9- and 10-membered heterocycles.

Whilst this section has shown that methodologies that access to indole- or benzofuran-fused medium-sized heterocycles are gradually emerging, examples that include other heteroarenes (e.g. pyrrole-annulated medium rings) are rare and, in many instances, are limited to the formation of 7-membered ring analogues.[150-154] It is conspicuous that little progress has been made to broaden the range of heteroaromatic units that can be fused to medium rings, which, in turn, would enable increased entry to pharmaceutically relevant chemical space. Hence, new methods are urgently required and ideally

these would proceed in a direct, atom economical, diversity-orientated and stereocontrolled manner. With these factors in mind, studies into the newly discovered formation of heterocycles **152a**/**153a** began (Scheme 40). The project was conducted in collaboration with Dr G.-W. Wang and his contributions are clearly indicated in the text and by footnotes under relevant Tables and Schemes.

2.4 Preliminary Optimisation and Reaction Scope

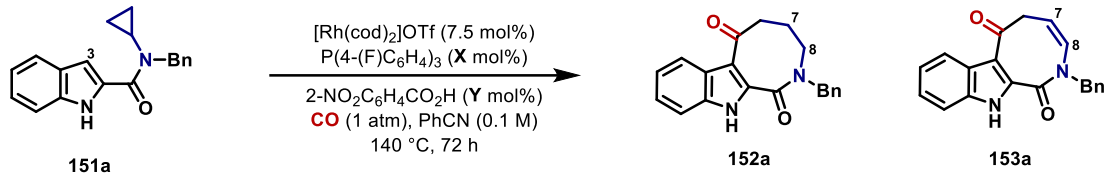
At the outset of this project, the initial objective was to optimise reaction conditions for the formation of sp^3-rich saturated heterocycle **152a**. As the factors governing the terminating step (*i.e.* protodemetallation or β-hydride elimination) remained unclear, a significant challenge would be controlling the oxidation level of the product (*i.e.* **152a** *vs.* **153a**). In an ideal scenario, it was hoped that complementary conditions would be achievable in order to selectively access either C7/8 saturated heterocycle **152a** or C7/8 unsaturated heterocycle **153a**. Key screening results from these optimisation studies are reported in Tables 1 and 2. The choice of solvent was found to be critical; changing from a coordinating solvent (*e.g.* PhCN) to non-coordinating solvent (*e.g.* 1,2-DCB) effectively inhibited formation of **152a** (Table 1, entries 1 *vs.* 2), suggesting that the solvent plays an important role in stabilising the Rh-centre. Other coordinating solvents were assessed (e.g. DMSO and valeronitrile) but none of these resulted in improved yield, presumably because they coordinated too strongly to the metal centre and thus prevented coordination of the directing group. Using PhCN as the solvent, various electron-deficient phosphine ligands were tested in the reaction, with $P(4\text{-}FC_6H_4)_3$ proving to be optimal (Table 1, entry 3). Increasing the loading of $2\text{-}NO_2C_6H_5CO_2H$ from 30 mol% to 100 mol% led to a further increase in yield of saturated heterocycle **152a** to 60% (Table 1, entry 7). In accordance with previous studies,[21] it was proposed that the acid additive serves as a proton source to facilitate the final protodemetallation step (*i.e.* **III** to **152a**, Scheme 40). Alternative cationic Rh(I)-catalysts, including $[Rh(cod)_2]BARF$ and $[Rh(cod)_2]BF_4$, resulted in reduced yield of saturated **152a** (Table 1, entries 8−9). Increasing or decreasing the reaction temperature (*e.g.* 130 °C *vs.* 140 °C *vs.* 150 °C) was also detrimental to the yield of heterocycle **152a**.



Entry	X	Solvent	Ligand	Y (mol%)	Remaining 151a[a]	Yield 152a[a]	Yield 153a[a]
1	OTf	PhCN	$P(C_6F_5)_3$	15	18%	18%[b]	18%
2	OTf	1,2-DCB	$P(C_6F_5)_3$	15	>95%	<5%	<5%
3	OTf	PhCN	$P(4\text{-}(F)C_6H_4)_3$	15	-	48%	10%
4	OTf	PhCN	$P(4\text{-}(F)C_6H_4)_3$	30	-	60%	23%
5	OTf	PhCN	$P(4\text{-}(CF_3)C_6H_4)_3$	30	<5%	41%	19%
6	OTf	PhCN	$P\text{-}(3,4,5\text{-}(F)_3C_6H_2)_3$	30	11%	57%	21%
7	OTf	PhCN	$P(4\text{-}(F)C_6H_4)_3$	100	-	60%[b]	15%
8	BARF	PhCN	$P(4\text{-}(F)C_6H_4)_3$	100	10%	20%	11%
9	BF_4	PhCN	$P(4\text{-}(F)C_6H_4)_3$	100	16%	11%	9%

Table 1: Selected optimisation results from the in the Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **151a**. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [b] Isolated yields.

In all the conditions evaluated so far, C7/8 saturated product **152a** was observed as the major product. Subsequently, it was hypothesised that further refinement of the acid and ligand loadings might improve the yield and selectively for **152a**. Notably, in the absence of the acid additive, only trace amounts of **152a** were formed (Table 2, entry 1). Additionally, when the phosphine ligand was omitted, the yield and selectivity of **152a** also decreased (24% yield, **152a**:**153a** = 1.0:1, Table 2, entry 2). These control experiments verified that both the acid additive and phosphine ligand are necessary for reactivity. Systematic examination of the acid loading (Table 2, entries 3−8) revealed that 150 mol% of $2\text{-}NO_2C_6H_5CO_2H$ increased the yield of **152a**, delivering the target molecule in 72% isolated yield and with moderate selectivity over **153a** (Table 2, entry 7, **152a**:**153a** = 5.0:1). The selectivity for saturated product **152a** was improved further by adjusting the ligand:catalyst ratio (1:1 *vs*. 2:1 *vs*. 3:1; Table 2, entries 7−9) with a 3:1 ratio providing product **152a** with excellent yield and selectivity. The optimised reaction conditions, as outlined in Table 2, entry 10, delivered heterocycle **152a** in 72% isolated yield and with 10:1 selectivity over unsaturated adduct **153a**.

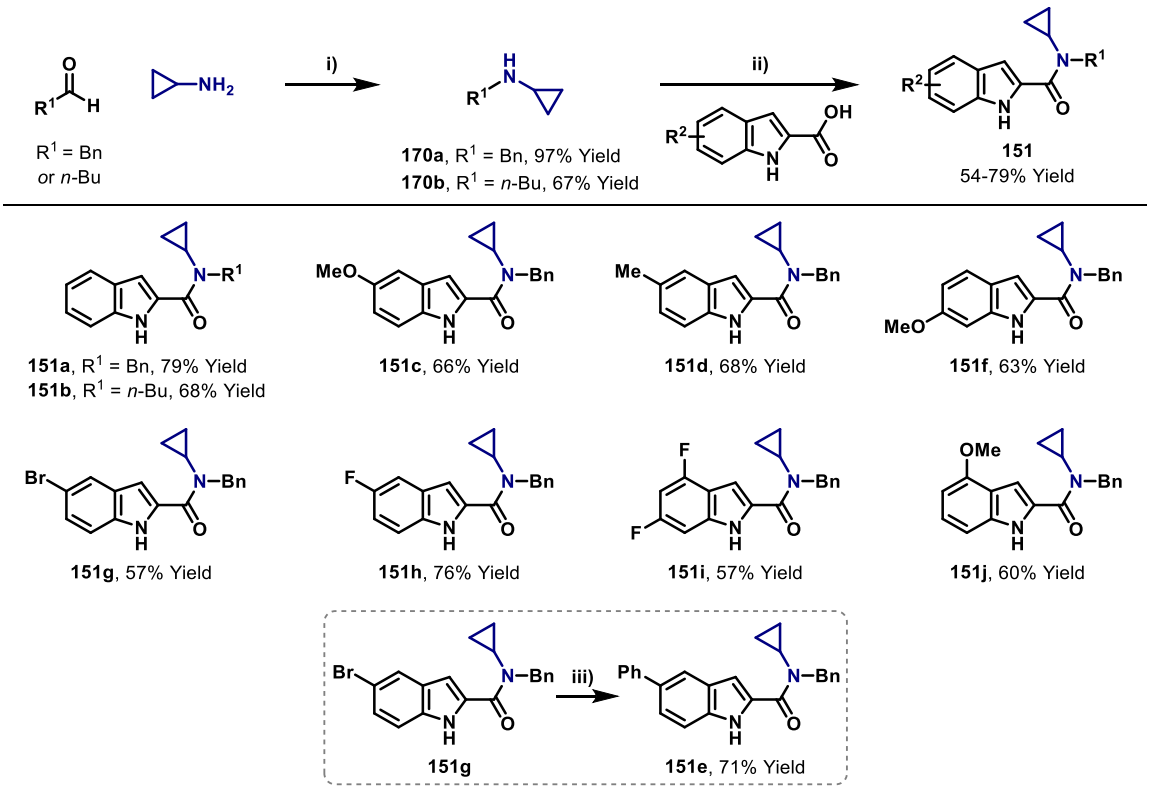


Entry	X (mol%)	Y (mol%)	Remaining 151a[a]	Yield 152a[a]	Yield 152a[a]	152a:153a
1	15	/	52%	<5%	<5%	n.d.
2	/	100	/	24%	24%	1.0:1
3	15	15	/	55%[b]	10%	5.5:1
4	15	30	/	60%	23%	2.5:1
5	15	50	/	38%	10%	4.0:1
6	15	100	/	60%[b]	15%	3.5:1
7	15	150	/	72%	15%	5.0:1
8	15	200	/	50%	8%	6.0:1
9	8.25	150	/	40%	11%	3.5:1
10	22.5	150	/	72%[b]	7%	10:1

Table 2: Evaluation of acid and ligand loadings in the Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **151a**. [a] The yields were determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [b] Isolated yields. The ratio of **152a**:**153a** was determined by ^{1}H NMR analysis of crude material.

2.4.1 Synthesis and scope of indole C2-cyclopropylamides

Having optimised the carbonylative cyclisation of indole **151a**, the scope of the reaction with respect to substituents on the indole unit was examined. To enable these studies, cyclopropylamide substrates **151b–h** were readily synthesised in a two-step process as shown in Scheme 45. Reductive amination of cyclopropylamine with either benzaldehyde or butyraldehyde delivered amines **170a** and **170b** in 67–97% yield. Subsequent EDCI-coupling of **170a**/**170b** with the corresponding carboxylic acid afforded **151a–d** and **151f–j** in moderate to good yield (57−79% yield, Scheme 45). In the case of phenyl derivative **151e**, the target molecule was obtained by Suzuki cross-coupling of bromo-**151g** with phenyl boronic acid which proceeded in 71% yield.



Scheme 45: Synthesis of indole C2-cyclopropylamides. *Reagents and conditions* i) corresponding aldehyde, $NaHCO_3$, MeOH, reflux, 18 h *then* $NaBH_4$, 0 °C to r.t., 18 h; ii) corresponding carboxylic acid, EDCI, DMAP, CH_2Cl_2, r.t. 8–18 h; iii) phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane/H_2O (3:1), 105 °C, 4 h, 71%.

With a selection of cyclopropylamides in hand, the generality of the new protocol was scrutinised (Table 3). Heterocyclisations of indole derivatives with electron-donating substituents (*e.g.* R^2 = methoxy, methyl, phenyl) proceeded efficiently, affording saturated heterocycles **152c**, **152d, 152e** and **152f** in 48%−60% yield, and with consistently good selectivity over the C7-8 unsaturated variants **153c**−**f** (7:1 to 12:1). In all cases, the saturated products **152c**−**f** could be easily separated from minor unsaturated products **153c**−**f** by column chromatography. Even C5-bromo derivative **152g** reacted, albeit in lower conversion, to afford **152g** in 25% yield, with the remaining mass balance consisting of a mixture of unreacted **151g** and protodebrominated **151g** (*i.e.* **151a**). Nevertheless, it is encouraging that the potentially labile C−Br bond of **151g** remained intact to facilitate post-cyclisation functionalisation. However, this method is not without its limitations; in particular, fluorinated analogues **151h** and **151i** showed no reactivity, indicating that electron-withdrawing substituents on the indole unit are not compatible. The same outcome was observed for C4-substituted substrates, such as methoxy bearing **151j**. The lack of reactivity of **151j** could be explained by unfavourable steric interactions between the C4-substituent and the requisite rhodacycle (*cf.* **II** and **III**, Scheme 40), which consequently inhibits formation of **152j**.

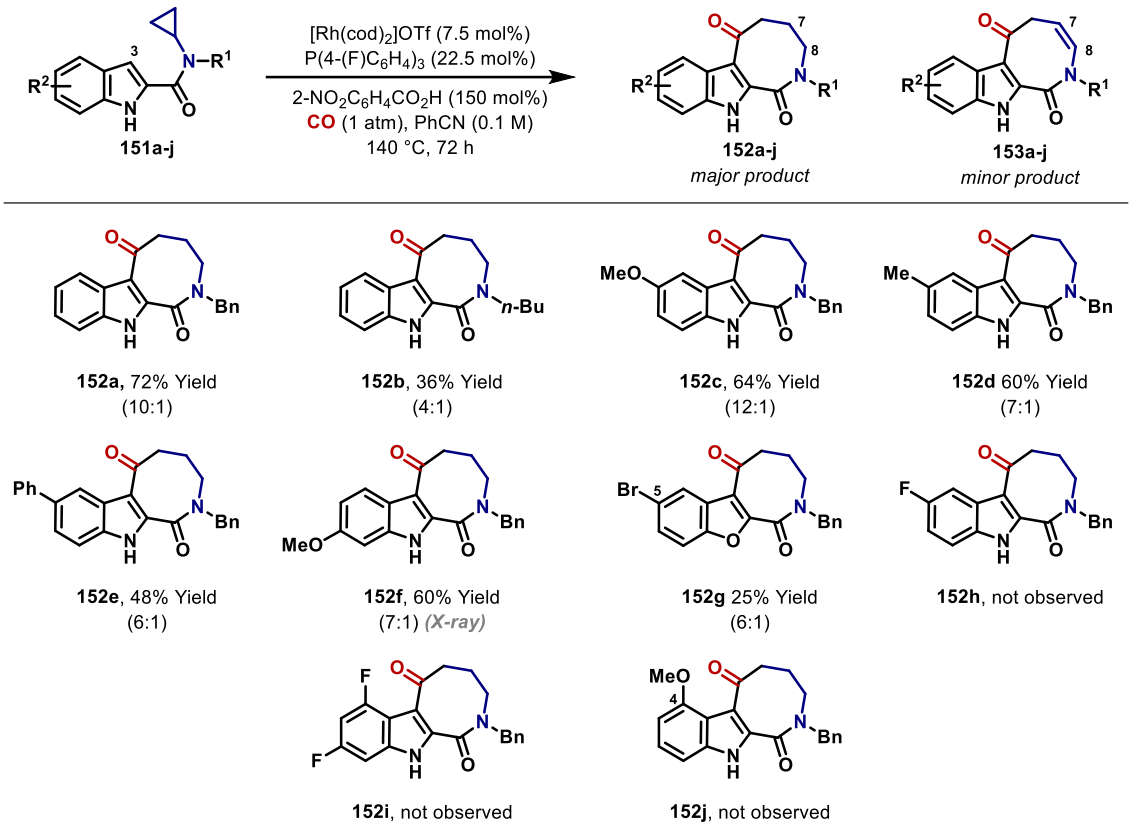
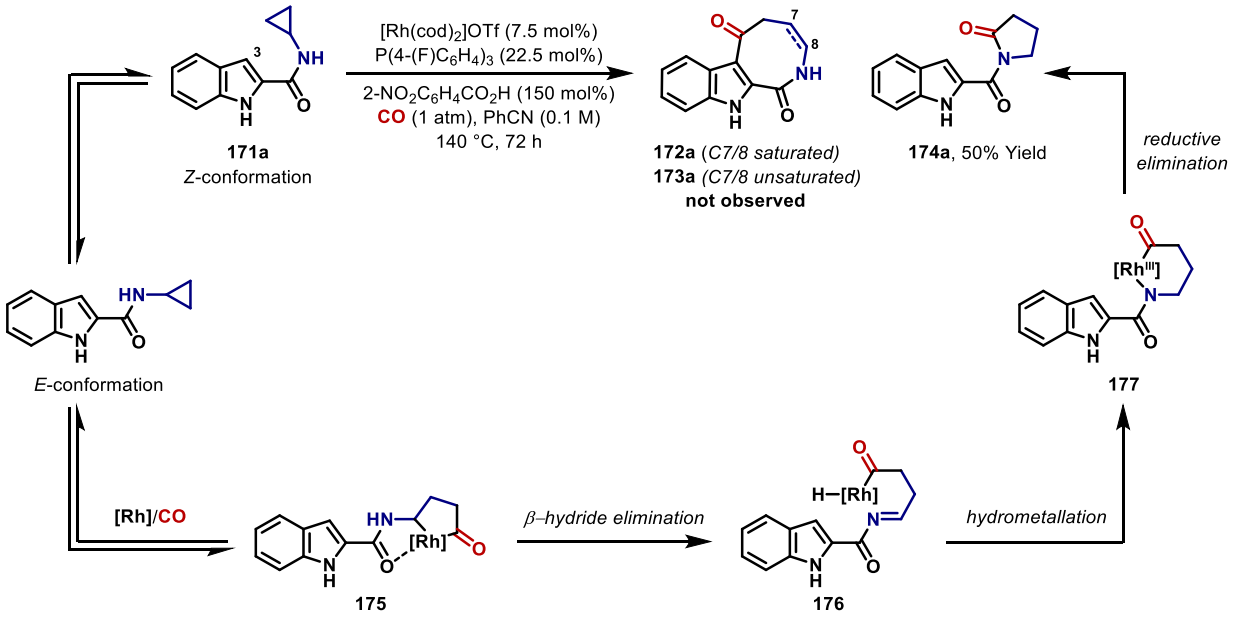


Table 3: Rh(I)-catalysed carbonylative cyclisation *via* the C-3 position of indole cyclopropylamides. Isolated yields of the major product are given. The ratio of **152a–j**:**153a–j** was determined by ^{1}H NMR analysis of crude material and is given in parentheses.

All of the carbonylative heterocyclisations described in this section have employed tertiary cyclopropylamide substrates. Therefore, to determine if secondary cyclopropylamides are compatible substrates, *N*−H cyclopropylamide **171a** was subjected to the new protocol. In the event, expected 8-membered heterocycles **172a**/**173b** were not observed; instead γ-lactam **174a** was isolated as the sole product in 50% yield (Scheme 46). Although the exact mechanism for the formation of γ-lactam **174a** remains unclear, one possible mechanism is outlined in Scheme 46, and involves initial formation of rhodacyclopentanone **175**. However, unlike in the previous examples (*cf.* rhodacyclopentanone **II**, Scheme 40), it was speculated that rhodacyclopentanone **175** can undergo β-hydride elimination *via* the N-H unit to deliver enamide **176** with a tethered Rh(III)-hydride moiety. From here, hydrometallation leads to 6-membered rhodacycle **177** and then C−N reductive elimination delivers the observed γ-lactam product **174a**. Presumably this reaction pathway is favoured because complex **175** is stable; therefore, rotation around the amide unit is less likely as it would bring the rhodacyclopentanone into close proximity with the indole unit. The change in reaction outcome reinforces the original design hypothesis that restricted conformational freedom of the endocyclic amide unit is required to access the necessary metallabicycle (*i.e.* **II** to **III**, Scheme 40). The synthesis of γ-lactams by Rh(I)-catalysed carbonylative ring-expansion of aminocyclopropanes has previously been reported in the literature.[155]

A comparison with this method and subsequent investigations into the synthesis of related γ-lactams will be addressed in Section 3.3.



Scheme 46: Proposed mechanistic pathway for the formation of γ-lactam **174a** by the Rh(I)-catalsyed carbonylative cyclisation of secondary cyclopropylamide **171a**.

2.4.2 Evaluation of alternative heteroaromatic C2-cyclopropylamides

Encouraged by the successful cyclisation of indole derivatives **151a**–**g**, the protocol was extended to other classes of heteroarenes. C2-cyclopropylamides **151k**–**n** were synthesised following the equivalent two-step procedure described for indole derivatives **151** (*cf.* Scheme 45, see Section 7.3.1 for further details). Pyrrole (**151k**), furan (**151l**) and thiophene (**151m**) systems participated in the transformation to provide C7/8 saturated heterocycles **152k**–**m** in moderate to good yield (24–48%, Table 4) and with moderate levels of selectivity over unsaturated heterocycles **153k**–**m** (4:1 to 6:1). Of note, the yield of these systems corresponds with the nucleophilicity of heteroaromatic unit (pyrrole>furan>thiophene),[156] suggesting that perhaps the C(sp^2)−H metallation step proceeds *via* electrophilic aromatic substitution (*i.e.* from **II** to **III**, Scheme 40) and not a concerted metallation deprotonation (CMD) type pathway. On the other hand, while the conversion of *N*-methyl pyrrole **151n** to heterocycles **152n** and **153n** was high, selectivity was low (combined yield of 72%, **152n**:**153n** = 2:1). This result suggests that a more electron rich heteroarene promotes β-hydride elimination over C8-protodemetallation. However, the exact reason for the different product ratios obtained by simply methylating the starting material cannot be easily explained (*N*−H pyrrole **152k**:**153k**, 6:1 *vs.* *N*-methyl pyrrole **152n**:**153n**, 2:1**)**. It was postulated that an electron-rich heteroarene may facilitate β-hydride elimination by enhancing the developing cross-conjugation between the arene and C7−C8 double bond. This interpretation must be treated with caution and alternative mechanistic pathways for the formation

of **153n** cannot be discounted (see Section 2.6 for further discussion). Regardless, the reduced selectivity for the formation of *N*-methyl pyrrole **152n** was not considered a major restriction (owing to the ease of installation the methyl group from NH-pyrrole **152k**) and without doubt, NH-pyrrole **152k** is a more synthetically flexible target.

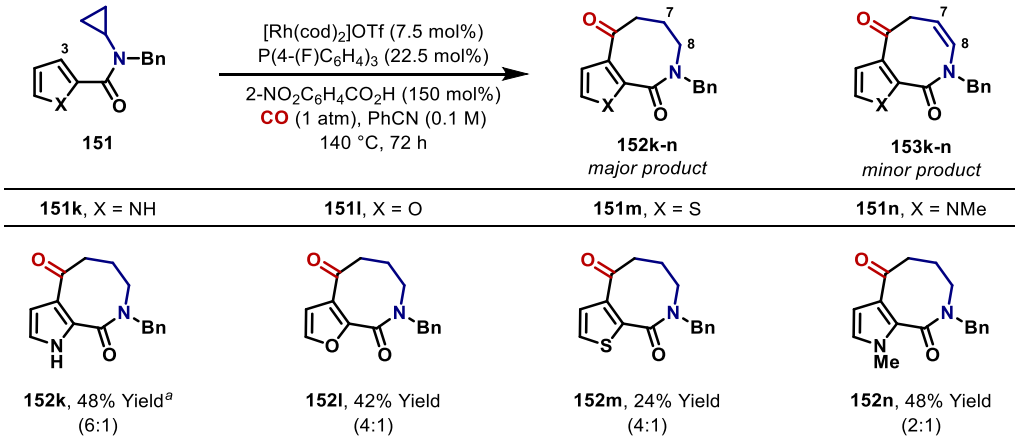


Table 4: Evaluation of alternative heteroaromatic C2-cyclopropylamides. Isolated yields of the major product are given. The ratio of **152k**–**n**:**153k**–**n** was determined by ^{1}H NMR analysis of crude material and is given in parentheses. [a] P(3,4,5-(F)$_3$C$_6$H$_2$)$_3$ (22.5 mol%) was used.

2.4.3 Evaluation of heteroaromatic C3-cyclopropylamides

The studies outlined so far form 8-membered ring heterocycles *via* the C3 position of the heteroarene unit. Five-membered heteroaromatics are nucleophilic *via* C2 and C3; consequently, it was proposed that complementary processes might be achieved by attaching the cyclopropylamide unit to the C3 position, which, in turn, would allow for cyclisation *via* the C2 position of the heteroarene. To test this hypothesis, indole **178a** was readily prepared (see Section 7.3.1) and under the established Rh(I)-catalysed carbonylation protocol, C7/8 saturated heterocycle **179a** was formed in 42% yield with moderate selectivity over alkene **180a** (Table 5, **179a**:**180a** = 4:1). Pleasingly, the process extended to other heteroaromatics, as demonstrated by the cyclisation of **178b**–**e**, which generated **179b**–**e** in synthetically useful yields (24−67% yield). Significantly for products **179c**–**e** competing cyclisation via C4 was not observed and the structure of **179e** was confirmed by single crystal X-ray diffraction. The processes in Table 5 offer distinct regioselectivity from those in Tables 3 and 4, such that depending on the substrate used, the position of the *N*-centre can easily be programmed into the 8-membered ring system.

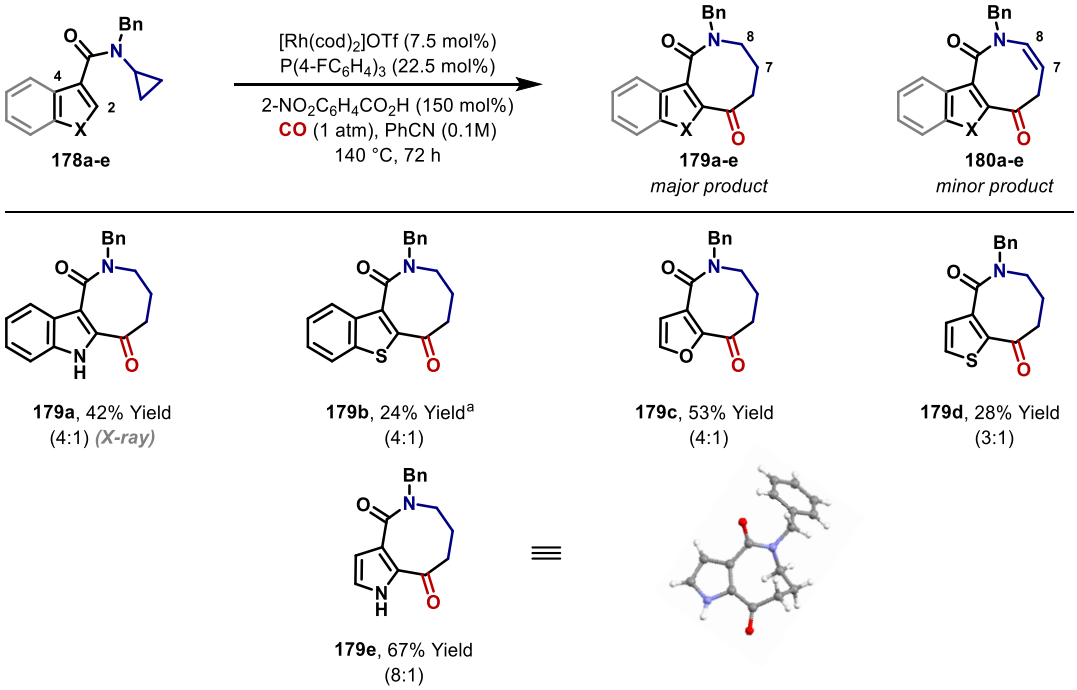
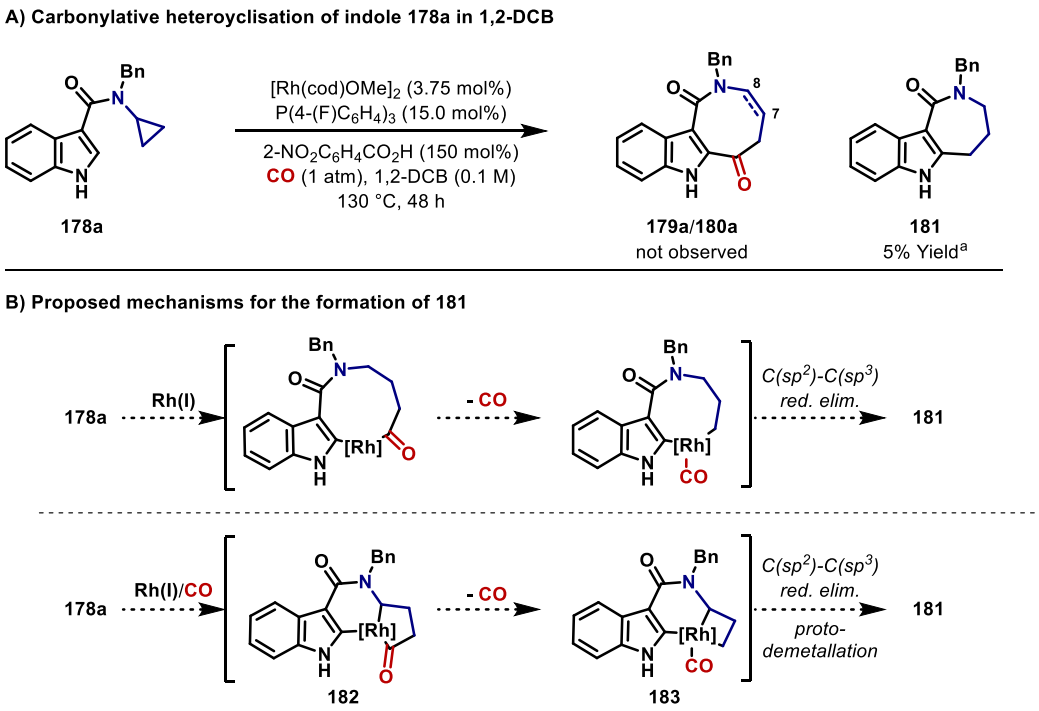


Table 5: Rh(I)-catalysed carbonylative cyclisation *via* the C-2 position of heteroaromatic cyclopropylamides. Isolated yields of the major product are given. The ratio of **179a**–**e**:**180a**–**e** was determined by ^{1}H NMR analysis of crude material and is given in parentheses. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

Taken on balance, the results obtained from this scope exploration did not reach our threshold for a robust and general protocol. In other words, even though the protocol could be applied to a wide range of heteroaromatic substrates, additional efforts were needed to fine-tune the yield and selectivity for the desired saturated products. It was therefore decided that that the reaction should be redeveloped from first principles. Thus, indole **178a** was selected for further optimisation studies and investigations to identify second generation conditions began.

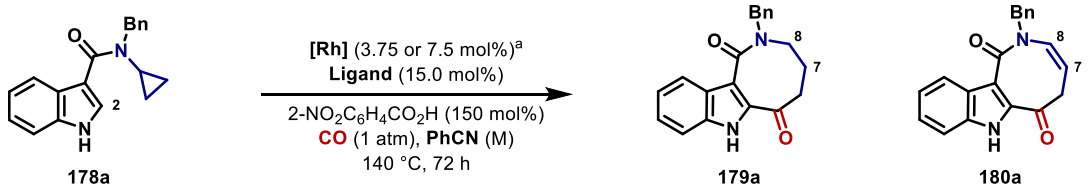
2.5 Second Generation Optimisation Studies

First, a simple survey of reaction solvents (DMF, DMSO, valeronitrile) was undertaken, but no desired product was observed in these reactions, and indole **178a** either degraded or did not react. Interestingly, substitution of PhCN for 1,2-DCB (a non-coordinating solvent) afforded 7-membered heterocycle **181** in 5% *in situ* yield (Scheme 47). It is unclear exactly how heterocycle **181** forms, but one possibility might involve extrusion of CO *via* insertion of the Rh(I)-catalyst into the acyl–C(sp^2) bond of **179a** (Scheme 47A).[69] Alternatively, a rhodacyclobutane-based pathway might be operational (Scheme 47B). In this scenario, directed formation of rhodacycle **182** is followed by extrusion of CO to give intermediate **183**. From here, C(sp^2)–Csp^3) reductive elimination and protodemetallation affords 7-membered heterocycle **181**. Investigations into the feasibility of these mechanistic proposals are discussed in more detail in Section 2.7.2.



Scheme 47: Rh(I)-catalysed carbonylative heterocyclisation of indole **178a** in 1,2-DCB delivered 7-membered heterocycle **181**. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

Returning to the primary task of improving the yield and selectivity of **179a**, a number of electron-deficient ligands were evaluated in PhCN with $[Rh(cod)_2]OTf$, but none of these improved the yield of heterocycle **179a** (Table 6, entries 1–4). Different cationic Rh(I)-sources, including $[Rh(cod)_2]BARF$ and $[Rh(cod)_2]BF_4$, also failed to increase the yield (Table 6, entries 5–6). Subsequently, a range of neutral Rh(I)-catalysts, (e.g. $[Rh(cod)OMe]_2$, $[Rh(cod)OH]_2$ and $[Rh(cod)Cl]_2$, Table 6, entries 7–9) were trialled. It was found that switching to $[Rh(cod)OMe]_2$ provided a breakthrough, with the target heterocycle **179a** isolated in 58% yield and with improved selectivity over **180a** (**179a**:**180a** = 6.5:1, Table 6, entry 9). Presumably the methoxide ligand can exchange more effectively with the acid additive to form an active Rh(I)-carboxylate catalyst.[157] In line with these thoughts, a wide array of acid additives (e.g. $AdCO_2H$, fumaric acid, diphenyl acetic acid, hexanoic acid and electronically distinct benzoic acid derivatives) was screened. In general, good efficiency was maintained with these acid additives (typically 45–72 % *in situ* yield of **179a**) but none offered significant advantages over $2\text{-}NO_2C_6H_5CO_2H$ with respect to selectivity for C7/8 saturated **179a** (typically **179a**:**180a** = 2:1). Additionally, these studies revealed no trends with respect to the steric environment, acidity or the coordinating ability of the acid additive; therefore, as $2\text{-}NO_2C_6H_5CO_2H$ offered the highest levels of selectivity, optimisation studies continued with this acid.



Entry	[Rh]	Ligand	Conc.	Remaining 178a[b]	Yield 179a[b]	Yield 180a[b]	179a:180a
1	$[Rh(cod)_2]OTf$	$P(4\text{-}(F)C_6H_4)_3$	0.1 M	<5%	42%[c]	10%	4.0:1
2	$[Rh(cod)_2]OTf$	$P(4\text{-}(CF_3)C_6H_4)_3$	0.1 M	-	34%	5%	7.0:1
3	$[Rh(cod)_2]OTf$	$P(C_6F_5)_3$	0.1 M	-	17%	4%	4.0:1
4	$[Rh(cod)_2]OTf$	$P\text{-}(3,4,5\text{-}(F)_3C_6H_2)_3$	0.1 M	-	24%	5%	5.0:1
5	$[Rh(cod)_2]BARF$	$P(4\text{-}(F)C_6H_4)_3$	0.1 M	15%	18%	11%	1.5:1
6	$[Rh(cod)_2]BF_4$	$P(4\text{-}(F)C_6H_4)_3$	0.1 M	20%	26%	10%	2.5:1
7	$[Rh(cod)Cl]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.1 M	-	14%	17%	1.0:1
8	$[Rh(cod)OH]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.1 M	-	40%	6%	6.5:1
9	$[Rh(cod)OMe]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.1 M	-	58%[c]	9%	6.5:1
10	$[Rh(cod)Cl]_2$[d]	$P(4\text{-}(F)C_6H_4)_3$	0.1 M	-	58%	9%	6.5:1
11	$[Rh(cod)OMe]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.2 M	-	56%	7%	8.0:1
12	$[Rh(cod)OMe]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.3 M	-	56%	6%	9.5:1
13	$[Rh(cod)OMe]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.4 M	-	44%	9%	6.5:1
14	$[Rh(cod)OMe]_2$[e]	$P(4\text{-}(F)C_6H_4)_3$	0.3 M	-	58%[c]	6%	10.0:1

Table 6: Selected optimisation results from the Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **179a**. The ratio of **179a**:**180a** was determined by ^{1}H NMR analysis of crude material. [a] 3.75 mol% was used for dimeric Rh(I)-catalysts and 7.5 mol% was used for monomeric Rh(I)-catalysts. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [c] Isolated yields. [d] 20 mol% silver benzoate used as an additive. [e] The reaction temperature was 130 °C.

A key reaction parameter that had not been investigated so far was the reaction concentration. Interestingly, increasing the concentration (0.1 M *vs.* 0.2 M *vs* 0.3 M) had a beneficial effect on the ratio of **179a**:**180a** (Table 6, entries 9 and 11–12). When the reaction was carried out 0.3 M, saturated product **179a** was obtained in slightly diminished yield of 56%, but improved levels of selectivity were achieved (**179a**:**180a** = 9.5:1, Table 6, entry 12). Increasing the concentration from 0.3 M to 0.4 M was detrimental to the yield of **179a** (Table 6, entry 13). Whereas, lowering the reaction temperature to 130 °C at 0.3 M afforded the target saturated heterocycle in 58% yield and with 10:1 selectivity over the unsaturated product **180a** (Table 6, entry 14). No further improvement in yield was achieved through variation of these or other reaction components. Compared to the first generation conditions (see Table 2), the second generation conditions (as outlined in Table 6, entry 14) afforded the target saturated

heterocycle **179a** in a superior yield (58% *vs.* 44%) and more critically with enhanced selectivity over the unsaturated adduct **180a** (4:1 *vs.* 10:1). These improvements were achieved by replacing $[Rh(cod)_2]OTf$ with $[Rh(cod)OMe]_2$ and increasing the concentration of the reaction mixture.

2.6 Evaluation of second generation conditions

Having established an upgraded protocol, the second generation conditions were used to reinvestigate the scope of the (7+1) carbonylation cyclisation (Table 7). For comparative purposes, the yields and product ratios obtained under the cationic Rh(I)-catalysed conditions developed in Section 2.4 are quoted in square brackets.

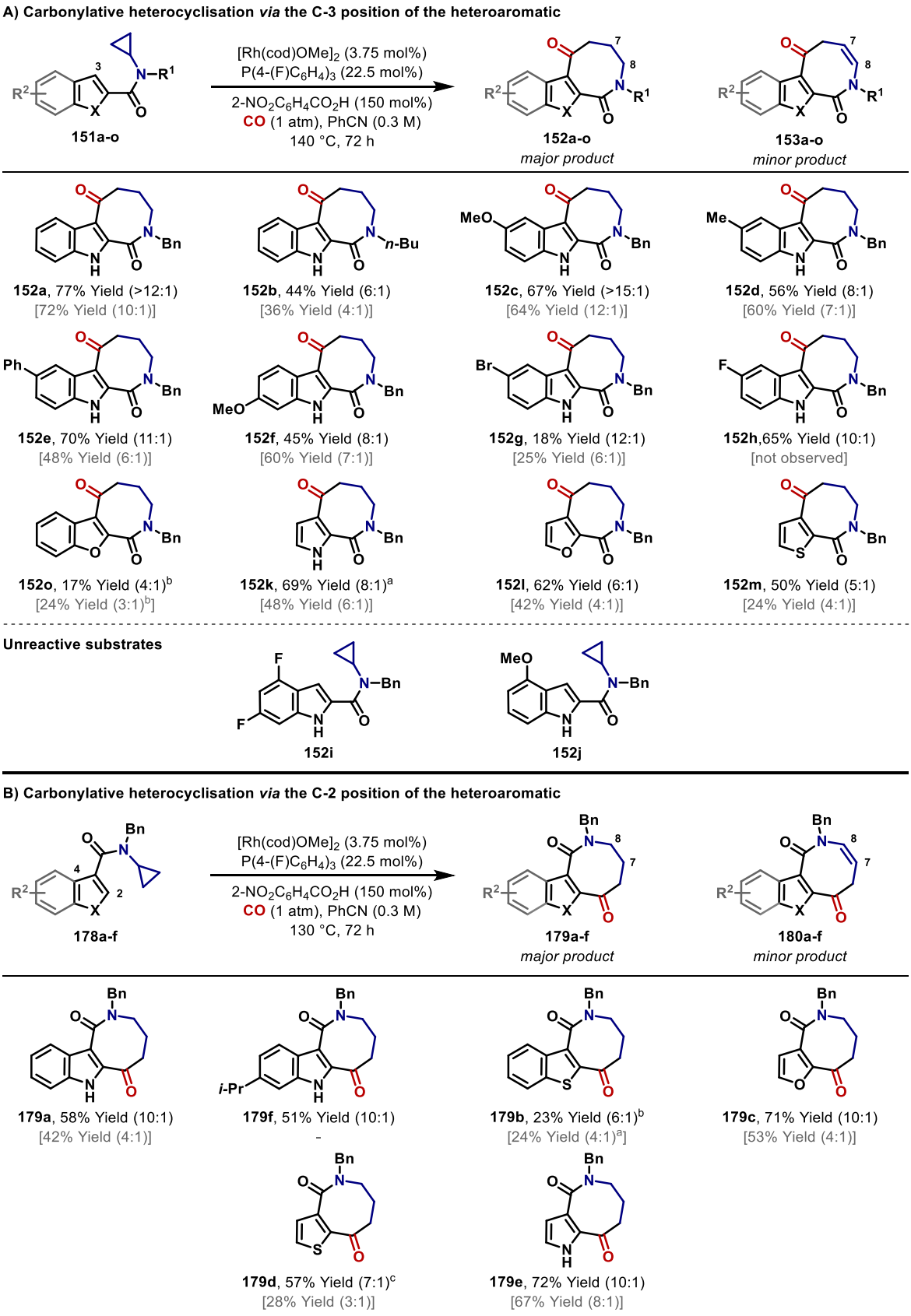
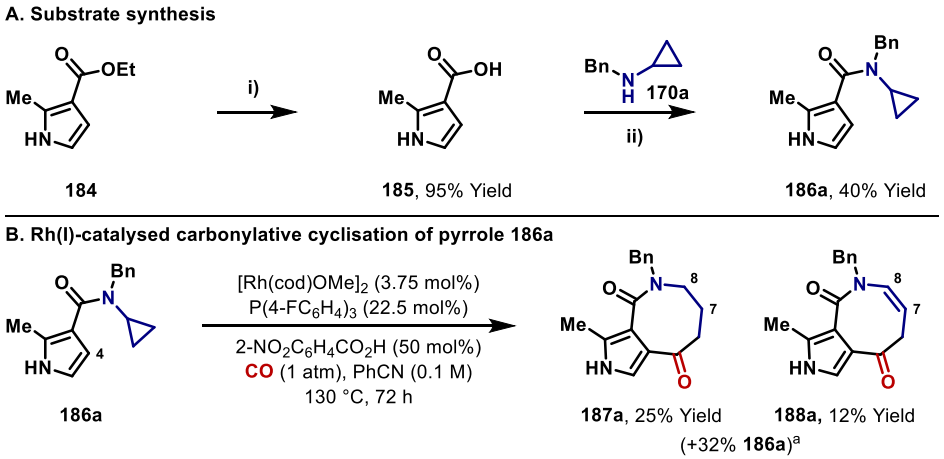


Table 7: Evaluation of second generation catalysis conditions. Isolated yields of the major product are given. The ratio of **152a–o**:**153a–o** and **179a–f**:**180a–f** was determined by ^{1}H NMR analysis of crude material and is given

in parentheses. The yield of **152a**–**n**/**179a**–**e** and ratio **152a**–**n**:**153a**–**n**/**179a**–**e**:**180a**–**e** using first generation conditions is reported in square brackets. [a] $P(3,4,5\text{-}(F)_3C_6H_2)_3$ (22.5 mol%) was used. [b] The yield was determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [c] The reaction temperature was 140 °C.

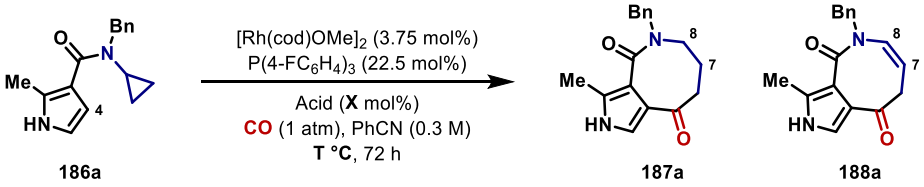
Under the new conditions, cyclisation *via* the C3 position of electronically distinct indoles provided adducts **152a–f** and **152h** in moderate to excellent yield (44–77%), and with good selectivity (8:1 to >15:1) over the corresponding C7/8 unsaturated variants **153** (Table 7A). Of note is the dramatic improvement in yield of fluorinated product **152h** (65% yield), which was previously not observed using the $[Rh(cod)_2]OTf$ catalyst system. Other classes of heteroarene also participated with greater efficiency. For example, heterocyclisation of thiophene **151m** proceeded smoothly to give **152m** in 50% isolated yield, compared to 24% under the first generation conditions. Likewise, cyclisation via the C2 position of heteroarenes **178c**–**f** afforded saturated adducts **179c**–**f** in good to excellent yield (51–72%) and with good selectivity over **180c**–**f** (Table 7B). However, limitations in the scope include benzofuran **152o**, aryl bromide **152g** and benzothiophene **179b**, which were generated in 17%, 18% and 23% yield respectively. In addition, attempted carbonylative cyclisation of C4-substituted indole substrates, such as difluoro analogue **151i** and methoxy analogue **151j**, delivered no product and unreacted starting material was recovered completely. Overall, despite these minor limitations, the new second generation conditions significantly increased the yield of the target heterocycles **152/179**, and considering the challenges associated with medium-sized closure, these results proved more than satisfactory.

To expand the synthetic versatility further, we next examined the carbonylative heterocyclisation of pyrrole **186a**, where the C2 position is blocked by a methyl group (Scheme 48). Exposure of pyrrole **186a**, prepared in two steps from pyrrole **184** and amine **170a** (Scheme 48A), to the $[Rh(cod)OMe]_2$/P-$(4\text{-}FC_6H_4)_3$/2-$NO_2C_6H_4CO_2H$ catalyst system provided C7/8 saturated heterocycle **187a** in 25% yield and unsaturated heterocycle **188a** in 12% isolated yield (Scheme 48B). The majority of the remaining mass balance consisted of unreacted pyrrole **186a** (32%).



Scheme 48: Preparation and Rh(I)-catalysed carbonylative cyclisation of pyrrole **186a**. A) *Reagents and conditions*; (i) LiOH.H_2O, 1,4-dioxane/H_2O, reflux, 4 hours, 95%; (ii) EDCI, DMAP (10 mol%), CH_2Cl_2, r.t., 16 h, 40%. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

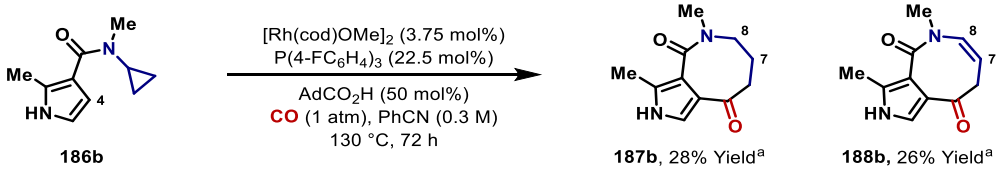
Attempts to improve the yield of C7/8 saturated heterocycle **187a** by evaluating the Rh(I)-pre-catalyst (*e.g.* $[Rh(cod)_2]OTf$, $[Rh(cod)_2]BARF$ or $[Rh(cod)OH]_2$), the phosphine ligand (electron-rich *vs*. electron-poor) and the reaction temperature (120 °C *vs.* 130 °C *vs.* 140 °C) provided no improvement. However, the replacement of 2-$NO_2C_6H_4CO_2H$ with $AdCO_2H$ gave a marked improvement in the reaction yield. Using 150 mol% of $AdCO_2H$, the total cyclisation yield was 58% with approximately equal amounts of heterocycles **187a** and **188a** (Table 8, entry 3). To address the selectivity issue, it was anticipated that altering the loading of $AdCO_2H$ would favour formation of saturated **187a**. However, whilst decreasing or increasing the loading of $AdCO_2H$ afforded **187a** with comparable yields, the selectivity over **188a** remained unchanged (*i.e.* **187a**:**188a** = 1:1, Table 8, entries 3–5).



Entry	Acid Additive	X (mol%)	T °C	Remaining 186a[a]	Yield 187a[b]	Yield 188a[a]	187a:188a
1[c]	2-$NO_2C_6H_4CO_2H$	150	140	0%	<5%[a]	<5%	n.d.
2[c]	2-$NO_2C_6H_4CO_2H$	150	130	0%	25%	12%[b]	2.0:1
3	AdCOOH	150	130	14%	37%	21%	1.0:1
4	AdCOOH	50	130	32%	39%	31%	1.0:1
5	AdCOOH	200	130	yes by TLC	37%	20%	1.0:1

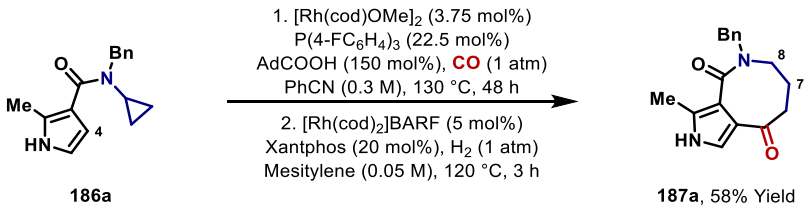
Table 8: Selected optimisation results from the Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **186a**. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [b] Isolated yields. [c] The reaction concentration was 0.1 M.

It was proposed that the poor selectivity for **187a** might have resulted from the steric bulk of the amide benzyl group preventing protodemetallation in the desired terminating step. Accordingly, replacement of the benzyl group of **186a** with a smaller methyl group was investigated. Against expectation, the heterocyclisation of *N*-methyl cyclopropylamide **186b** under [Rh(cod)OMe]$_2$/AdCO$_2$H conditions proceeded with similar efficiency and selectivity (Scheme 49). Heterocycles **187b** and **188b** were not isolated but assigned based on comparison with the benzyl variants **187a**/**188a**.



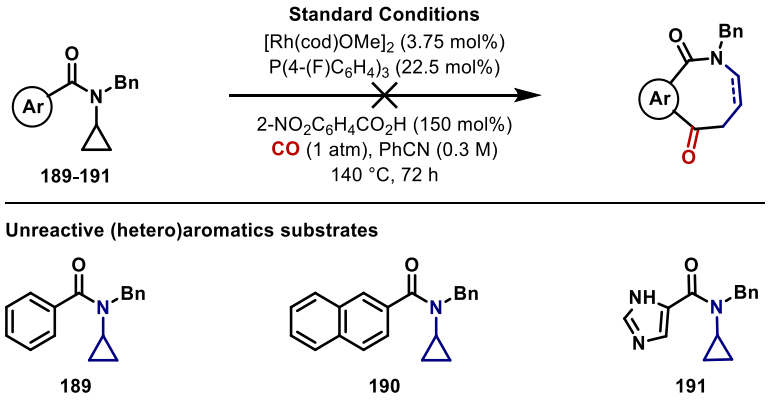
Scheme 49:Rh(I)-catalysed carbonylative cyclisation of pyrrole **186b**. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

As efforts to hone selectivity for the saturated product **187a** by virtue of the catalytic system and by design of the substrate proved ineffective, an alternative strategy was sought. To this end, following exposure of pyrrole **186a** to [Rh(cod)OMe]$_2$/AdCO$_2$H carbonylative conditions, the crude mixture was subjected to Rh(I)-catalysed hydrogenation conditions.[158,159] This procedural modification enabled smooth reduction of the enamide of **188a** and, in doing so, pyrrole **187a** was isolated in 58% yield for the two-step process (Scheme 50). Alternatively, reduction of the enamide of **188a** could be achieved using milder conditions. For example, hydrogenation of **188a** using Pd/C/H$_2$ (1 atm), afforded saturated heterocycle **187a** in 89% yield (more details are provided in Section 7.3.1).



Scheme 50: Two-step reaction sequence for the formation of pyrrole **187a**.

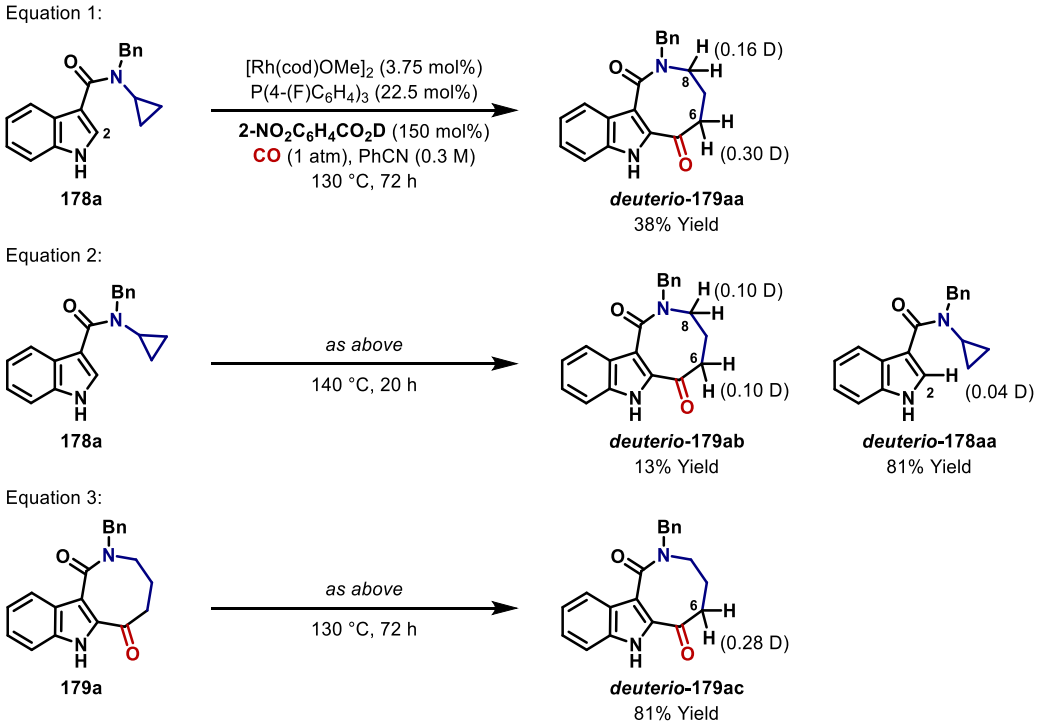
The heterocyclisations discussed so far all rely on electron-rich heteroarenes as the nucleophilic component. Therefore, to test the limits of the arene unit, phenyl-based systems **189** and **190** were explored; however, both substrates were unreactive under the standard catalytic conditions (Scheme 51). These results confirm that an electron-rich arene is essential for reactivity. Additionally, imidazole **191** was also found to be incompatible, presumably because the basic nitrogen atom coordinates to the Rh(I)-catalyst and deactivates it (Scheme 51).



Scheme 51: Evaluation of alternative (hetero)arene substrates.

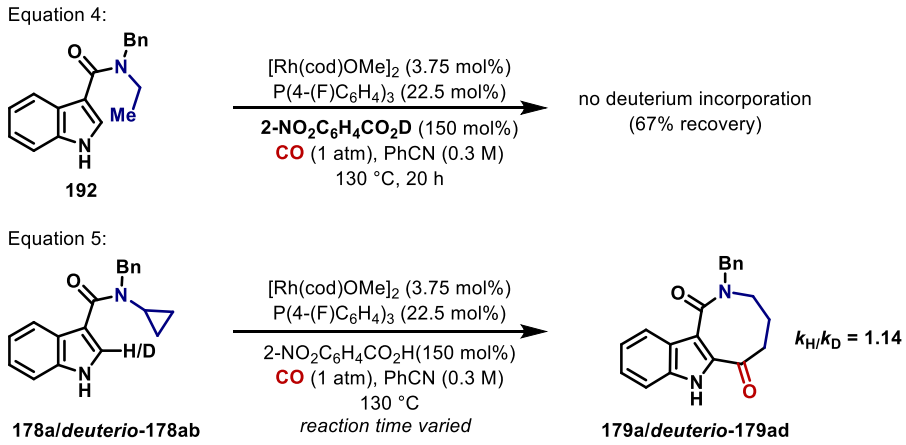
2.6 Mechanistic studies

At this stage, a series of experiments was undertaken to probe the mechanism of the reaction (Schemes 52 and 53). More specifically, we wanted to (i) elucidate the role of the acid additive and (ii) establish the first irreversible step of the transformation. To enable these studies, indole **178a** was selected because the signal corresponding to the C2-proton could be distinguished by ^{1}H NMR spectroscopy in d_3-acetonitrile. When the heterocyclisation of indole **178a** was run using 2-$NO_2C_6H_4CO_2D$ (prepared by dissolving 2-$NO_2C_6H_4CO_2H$ in d_4-methanol and concentrating *in vacuo* three times) deuterium incorporation was observed at C-6 (30% D) and C-8 (16% D) (***deuterio*-179aa**, Equation 1). At partial conversion, significantly lower levels of deuterium incorporation were observed at C-6 (10% D) and C-8 (10% D) (***deuterio*-179ab**, Equation 2). More importantly, ^{1}H and ^{2}D NMR analysis of recovered staring material from this experiment, revealed low levels of deuteration in ***deuterio*-178aa** at C-2 (4% D). Taken together, these observations are consistent with deuterium incorporation at C-8 occurring at the proposed protodemetallation step (*i.e.* **III** to **152a**, Scheme 40) and deuteration at the C-6 position occurring *via* enolisation of the product. To confirm the latter proposition, re-subjection of cyclised product **179a** to identical catalysis conditions led to 28% deuterium incorporation at C-6 (***deuterio*-179ac**, Equation 3).



Scheme 52: Mechanistic experiments.

The question remained as to how deuterium incorporation at C-2 of ***deuterio*-178aa** arises. To probe this, indole **192**, which lacks a cyclopropyl unit, was exposed to the Rh(I)-catalyst system in the presence of 2-$NO_2C_6H_4CO_2D$ (Equation 4). No deuterium incorporation was observed at the C2–H position, which seemingly rules out an exchange pathway involving carbonyl directed C-H activation of **178a**. Guided by this evidence and by previous reports,[21] we suggest that *reversible* carbonylative C–C bond activation to the rhodacyclopentanone (*i.e.* rhodacyclopentanone **I**, Scheme 40) precedes *reversible* C2–H metallation.

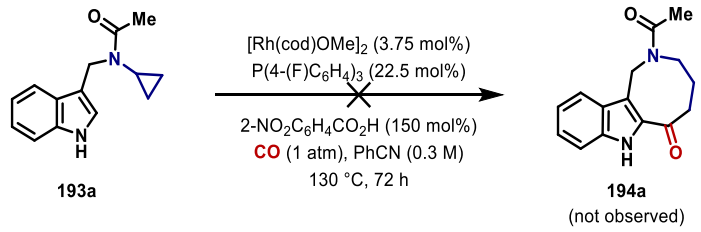


Scheme 53: Mechanistic experiments.

Further insight into the reaction mechanism was gained by stopping the reaction at specific time intervals with **178a** or ***deuterio*-178ab** and determining the conversion to product **179a**/***deuterio*-179ad**.

These studies revealed a relatively small kinetic isotope effect (k_H/k_D = 1.14, Equation 5),[160] suggesting that C–H metallation is not turnover limiting. Additionally, these observations are consistent with C–C reductive elimination being the first irreversible step, which might be due to the challenging ring size being formed. With this rationale in mind, more nucleophilic arenes may promote C–C reductive elimination by enhancing equilibrium access to the required metallacycle (*cf.* metallacycle **III**, Scheme 39). This notion is supported by (1) the efficiency trends observed for substrates **151k**–**m** (Table 4) and (2) the failure of phenyl-based systems to participate in the reaction (Scheme 51). The minor amounts of C7/C8 unsaturated products (**153a**–**o** and **180a**–**f**) observed throughout these studies could result from β-hydride elimination after the C–C reductive elimination step. In this instance, turnover might be achieved by protonation of the Rh(I)-hydride and reductive elimination of dihydrogen (see Schemes 33 and 40).[20,103]

Finally, the importance of an endocyclic amide directing group was confirmed by exposing *exo*-variant **193a** to the optimised conditions (Scheme 54). In this example, decomposition of starting material **193a** occurred and azocane **194a** was not observed. Overall, the mechanistic experiments outlined in this section are consistent with the proposed carbonylative cyclisation mechanism (Scheme 40) and corroborate previous observations by the Bower group.[21]



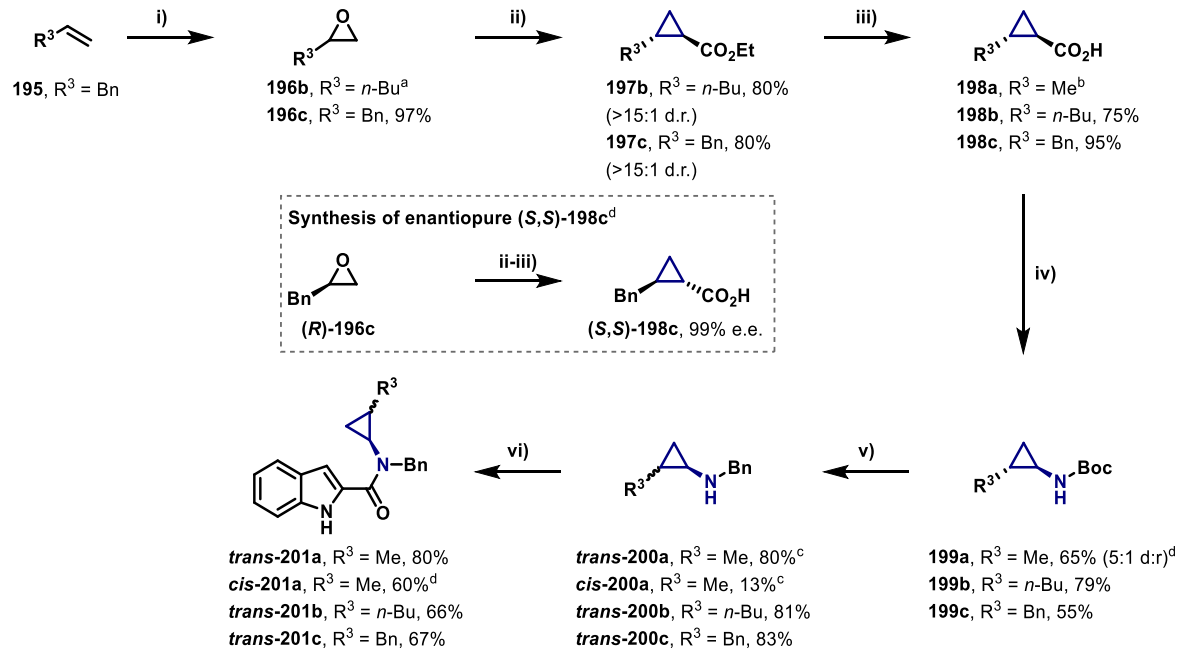
Scheme 54: Evaluation of *exo*-variant **193a** in the Rh(I)-catalysed carbonylation protocol.

2.7 Synthesis and scope of substituted aminocyclopropanes

Having gained a clearer understanding of the reaction mechanism, attention turned to evaluating 1,2-disubstituted cyclopropylamides under the new protocol. Key requirements for 1,2-disubstituted cyclopropane-based processes include: (1) regioselective generation of the rhodacyclopentanone intermediate and (2) transfer of this regiochemistry to the product. As discussed previously, directed rhodacyclopentanone formation from *trans*-1,2-disubstituted cyclopropanes occurs with high selectivity *via* the less hindered proximal C–C bond (see Section 1.3.1). Accordingly, it was envisaged that similar regioselectivity would be operative in the new heterocyclisation protocol and therefore, selective access to C-7 substituted products would be achievable. Additionally, substituted cyclopropanes are easily accessed in enantioenriched form, and so it was anticipated that stereospecific introduction of substituents on the 8-membered ring would be accomplishable.

2.7.1 Synthesis of cyclopropylamides containing 1,2-disubstituted cyclopropanes

A representative range of 1,2-disubstituted cyclopropylamide substrates was prepared by a previously developed route (Scheme 55).[16] First, epoxidation of allylbenzene **195** afforded benzyloxirane **196c** in good yield. Epoxides **196b**–**c** (**196b** was commercially available) then underwent a modified *trans*-selective Wadsworth-Emmons cyclopropanation with triethylphosphonoacetate to afford cycloproylesters **197b**–**c** in excellent yield.[161,162] Next, hydrolysis of cyclopropylesters **197b**–**c** provided the corresponding carboxylic acids **198b**–**c**. Subsequent Curtius rearrangement of carboxylic acids **198a**–**c** (**198a** was commercially available) with diphenylphosphoryl azide in *t*-BuOH delivered Boc-protected aminocyclopropanes **199a**–**c** in 55–79% yield.[163] TFA mediated Boc-deprotection of **199a–c**, followed by reductive amination with benzaldehyde gave *N*-benzyl amines ***trans*-200a**–**c** and ***cis***–**200a**. At this point, ***trans*-200a** and ***cis*-200a** were separated by column chromatography, thus allowing easy access to either diastereomer. EDCI coupling of *N*-benzyl cyclopropylamines ***trans*-200a–c**/***cis*-200a** with indole-1*H*-2-carboxylic acid afforded the 1,2-disubstuted cyclopropylamides ***trans*-201a**–**c**, ***cis*-201a** in 60–80%. Of note, enantioenriched *trans*-benzyl cyclopropylcarboxylic acid **(*S,S*)-198c** was formed from commercially available (*R*)-propylene oxide by a reported procedure.[164,165] Advancement to indole **(*S,S*)-201c** was achieved in a manner analogous to (***trans*)-201c**.

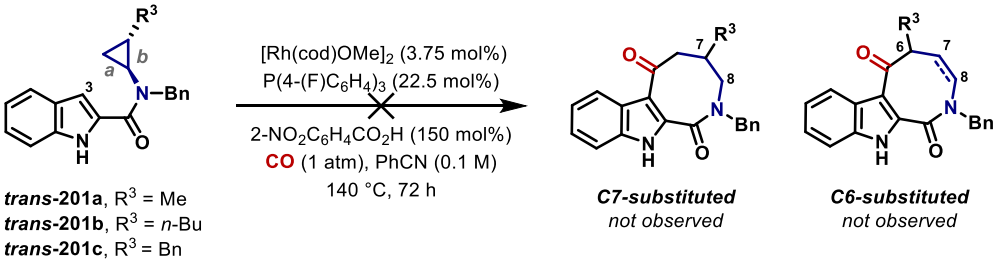


Scheme 55: Synthesis of 1,2-disubstituted aminocyclopropanes. *Reagents and conditions:* i) *m*-CPBA, CH_2Cl_2, 0 °C to r.t., 18 h; ii) triethylphosphonoacetate, *n*-BuLi, 1,2-dimethoxyethane, 130 °C, 18 h; iii) 4 M aq. NaOH, MeOH, r.t., 18 h; iv) diphenylphosphoryl azide, Et_3N, *t*-BuOH, 80 °C, 18 h; v) TFA, CH_2Cl_2, r.t., 2 h *then* benzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h *then* $NaBH_4$, 0 °C to r.t., 18 h; vi) indole-1*H*-2-carboxylic acid, EDCI, DMAP, CH_2Cl_2, r.t. [a] Commercially available. [b] Commercially available as a 4:1 (*trans:cis*) diastereomeric

mixture. [c] The *trans*- and *cis*-diastereomers were separated by flash column chromatography. [d] Synthesised by G.-W. Wang.

2.7.2 Evaluation of *trans*-1,2-disubstituted cyclopropylamides

With the required *trans*-1,2-disubstituted cyclopropylamides in hand, they were subjected to the second generation [Rh(cod)$_2$OMe] catalyst conditions (Scheme 56). Disappointingly, ***trans*-201a**–**c** all failed to undergo the desired heterocyclisation and in each case, substantial amounts of unreacted starting material was recovered. It was reasoned that the lack of reactivity exhibited by ***trans*-201a**–**c** stemmed from one overarching predicament: the increased steric demands of the systems impeded C–C bond activation. Using ***trans*-201b** as a model substrate, several key reaction parameters were re-evaluated such as catalyst ([Rh(cod)OMe]$_2$ *vs*. [Rh(cod)$_2$]OTf), phosphine ligand (electron-rich *vs*. electron-poor), acid additive (alternative benzoic acids and aliphatic acids) and temperature (130 °C *vs*. 140 °C *vs*. 150 °C). Unfortunately, ***trans*-201b** proved extremely resistant to C–C bond activation and no product arising from insertion into either the less hindered bond (*bond* ***a***) or the more hindered bond (*bond* ***b***) of ***trans*-201b** was detected under any of the conditions tried.



Scheme 56: Attempted Rh(I)-catalysed carbonylative cyclisation of *trans*-1,2-disubstituted cycloproproylamides ***trans*-201a**–**c**.

It was hypothesised that the endocyclic amide directing group of ***trans*-201a**–**c** might be facilitating insertion of the Rh(I)-catalyst into the N–H bond of the indole unit, and thereby rendering that catalyst inactive. Therefore, to circumvent this pathway and to gauge the impact of an *N*-substituent on promoting cyclisation, *N*-methyl ***trans*-202b**, *N*-benzyl ***trans*-203** and *N*-tosyl ***trans*-204** were prepared and evaluated in the heterocyclisation protocol using [Rh(cod)$_2$]OTf (Table 9).

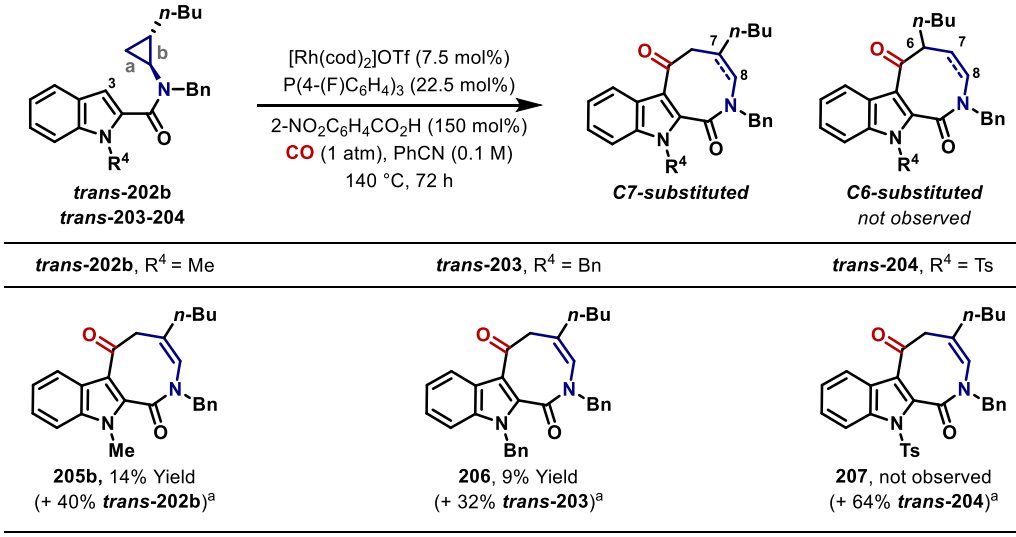
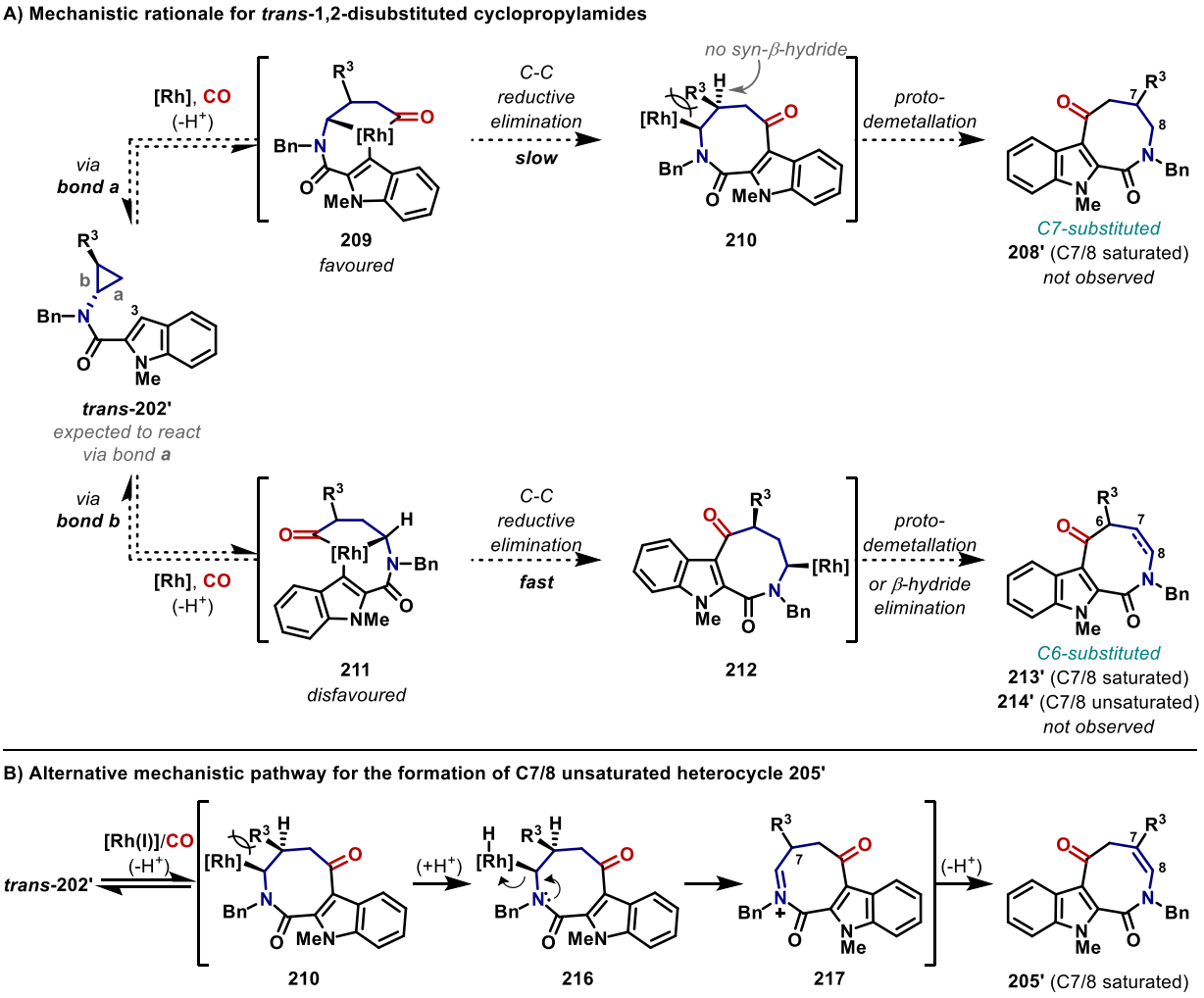


Table 9: Effect of *N*-indole substituents on the Rh(I)-catalysed carbonylative cyclisation of *trans*-1,2-disubstituted cyclopropylamides. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

Remarkably, *N*-methyl ***trans*-202b** cyclised *via* oxidative addition into the less hindered C–C bond (*bond* ***a*** of *N*-methyl ***trans*-202b**) in 14% yield to deliver unsaturated C7-substituted adduct **205b** as a single regioisomer. Increasing the steric bulk of the *N*-indole substituent had a detrimental effect on the yield (14% for *N*-methyl **202b** *vs*. 9% for *N*-benzyl **206**). No product was observed when *N*-tosyl ***trans*-204** was employed, confirming an earlier hypothesis that an electron-rich heteroarene is necessary (see Scheme 51). Additionally, in all cases, a low mass recovery of starting material was obtained, suggesting that the required rhodacyclic intermediates were potentially forming but decomposing prior to cyclisation. From a regioselectivity viewpoint, the sole formation C7-substituted heterocycles **205b**/**206** indicates that steric preferences of the system overrides the electronic preferences of C–C bond activation (*i.e.* the Rh(I)-catalyst inserts preferentially into *bond* ***a*** of ***trans*-202b**/***trans*-203**). Nevertheless, based on the studies described so far and from a mechanistic viewpoint, the exclusive formation of C7/8 *unsaturated* heterocycles **205b** and **206** was unexpected. To aid the understanding of this reaction outcome, the mechanistic pathways to C7-substituted heterocycles **205'**/**208'** and C6-substituted heterocycles **213'**/**214'** are examined in Scheme 57.



Scheme 57: Proposed mechanistic pathway for the Rh(I)-catalysed carbonylative heterocyclisation of *trans*-**202'**.

As depicted in Scheme 57, formation of C-7 regioisomer **208'** proceeds *via* initial oxidative addition of the Rh(I)-catalyst into the less hindered C–C bond (*bond* ***a***) of ***trans*-202'**, which, after C–H metallation forms metallacycle **209**. Subsequent C–C reductive elimination from intermediate **209** is most likely to be slow due to the ensuing steric clash between the Rh-centre and the C-7 substituent. From intermediate **210**, only protodemetallation is permissible to give saturated heterocycle **208'**. Alternatively, the formation of C-6 regioisomers **213'** and **214'** might occur and in this scenario, Rh(I)-addition to the more hindered C–C bond (*bond* ***b***) of ***trans*-202'** affords the kinetically disfavoured metallacycle **211.** From intermediate **211**, C–C reductive elimination to the C-6 regioisomer **212** is most likely to be faster (*cf.* **210**, 1,2- *vs.* 1,3-relationship) and terminating protodemetallation or β-hydride elimination gives heterocycles **213'** or **214'**. However, neither of these mechanistic pathways can account for the formation of C7/8 unsaturated heterocycles **205b**/**206** as there is no *syn-β-hydride* available at the stage of metallacycle **210**. Consequently, it was speculated that the formation of these products might be rationalised by invoking the nitrogen lone pair of the amide unit (Scheme 57B). In this scenario, following formation of intermediate **210**, oxidative protonation of the

Rh-centre triggers the nitrogen lone pair to eliminate a Rh(I)-hydride species to give iminium ion **217**. This elimination might be promoted by the relief of unfavourable steric interactions between the R^3 substituent and Rh-centre, and also facilitated by a relatively electron-poor cationic Rh(III)-hydride leaving group. Tautomerisation of **217** would then provide unsaturated heterocycle **205'**.

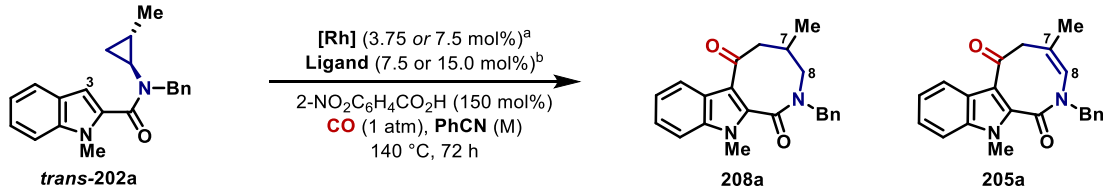
However, despite this rationale, the exclusive formation of C7/8 unsaturated variants **205b** and **206** is still unexpected. Indeed, as shown previously in Table 7, the C7/8 unsaturated analogues **153**/**180** were formed as the minor product during the evaluation of simple cyclopropylamides. As such, the question was raised as to how to account for the absence of the C7/8 saturated heterocycles **208'** (or **213'**) when 1,2-disubstituted cyclopropylamides were subjected to the catalytic protocol. The mechanistic studies discussed in Section 2.4 support the formation of C7/8 saturated heterocycles occurring *via* protodemetallation of an alkyl-Rh(I) intermediate However, it is conceivable that generation of these products might arise *via* hydrometallation of the C7/8 unsaturated adducts (*i.e.* **205'**) with a Rh(III)-hydride species. With this in mind, it was speculated that following Rh(I)-addition to ***trans*-202'** and CO insertion (*cf.* rhodacyclopentanone **II**, Scheme 40), decomposition to an *N*-vinyl amide *via* β-hydride elimination might occur more readily than the desired C–H metallation (*i.e.* **210** to **208'**). Assuming Rh(III)-H is released reversibly, then competition arises between the speculative *N*-vinyl amide and the unsaturated product **205'** with regards to subsequent hydrometallation.

In addition to these factors, the mechanistic insights outlined in Section 2.4, support the notion that the C–C reductive elimination step (*i.e.* **III** to **152a**, Scheme 40) is the first irreversible step. In the case of 1,2-disubstituted cyclopropylamides, an extra layer of complexity is added to this step due to the unfavourable steric interactions between the Rh-centre and the R^3 substituent, thus making it even more challenging. To combat this issue, third generation reaction conditions were sought to (1) promote C–C reductive elimination and (2) promote protodemetallation in the terminating step.

2.7.3 Third generation optimisation studies of challenging substrate *trans*-202a

Following this unanticipated result, *trans*-1,2-disubstituted cyclopropylamide ***trans*-202a** was selected as a pilot substrate for further optimisation studies. In collaboration with G.-W. Wang, over 200 reaction conditions were evaluated and the most significant findings are presented in Tables 10 and 11. First, neutral Rh(I)-sources, including $[Rh(cod)OMe]_2$ and $[Rh(cod)Cl]_2$, were evaluated, with both catalysts improving the yield of C7/8 unsaturated product **205a** compared to cationic $[Rh(cod)_2]OTf$ (24% for $[Rh(cod)OMe]_2$ and 17% for $[Rh(cod)Cl]_2$ *vs.* 7% for $[Rh(cod)_2OTf]_2$, Table 10, entries 1–3). Next, it was envisaged that the inclusion of a sterically demanding phosphine ligand might promote faster C–C reduction elimination and/or suppress β-hydride elimination and hence promote formation of saturated heterocycle **208a**. Strikingly, replacement of $P(4\text{-}FC_6H_5)_3$ with (*rac*)-BINAP afforded a mixture of C7/8 *saturated* heterocycle **208a** as the major product in 20% yield and C7/8 *unsaturated* heterocycle **205a** as the minor product in 13% yield (Table 10, entry 4). Following this promising result, over 20

commercially available bidentate phosphine ligands were screened, but no increase in yield or selectivity for product **208a** was achieved. Even more intriguingly, in the absence of (*rac*)-BINAP products **208a** and **205a** were obtained with similar levels of efficiency (20% and 11% yield respectively, Table 10, entry 5). In comparison, when 2-$NO_2C_6H_4CO_2H$ was omitted, the saturated product **208a** was not observed (Table 10, entry 6). These control experiments underpin the synergistic role of the acid additive as (1) a proton source to aid protodemetallation as the terminating catalytic step (*i.e.* the conversion of **210** to **208'**, Scheme 57A) and (2) as a ligand to stabilise off-cycle Rh-species.

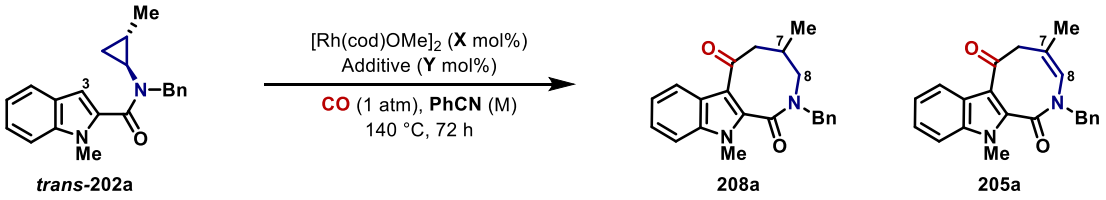


Entry	[Rh]	Ligand	Conc.	Remaining *trans*-202a[c]	Yield 208a[c]	Yield 205a[c]
1	$[Rh(cod)_2]OTf$	$P(4\text{-}(F)C_6H_4)_3$	0.10 M	29%	-	7%
2	$[Rh(cod)OMe]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.10 M	18%	-	24%
3	$[Rh(cod)Cl]_2$	$P(4\text{-}(F)C_6H_4)_3$	0.10 M	32%	-	17%
4[e]	$[Rh(cod)OMe]_2$	*rac*-BINAP	0.30 M	25%	20%[d]	13%
5[e]	$[Rh(cod)OMe]_2$	/	0.67 M	-	20%	11%
6[e,f]	$[Rh(cod)OMe]_2$	*rac*-BINAP	0.67 M	46%	-	10%

Table 10: Selected results from the optimisation of challenging substrate cyclopropylamide ***trans*-202a**. [a] 3.75 mol% was used for dimeric Rh(I)-catalysts and 7.5 mol% was used for monomeric Rh(I)-catalysts. [b] 7.5 mol% *rac*-BINAP *or* 15.0 mol% $P(4\text{-}(F)C_6H_4)_3$ was employed. [c] Yields were determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [d] Isolated yield. [e] Results obtained by G.-W. Wang. [f] 2-$NO_2C_6H_4CO_2H$ was omitted.

Optimisation studies next focussed on screening alternative acid additions. Replacement of 2-$NO_2C_6H_4CO_2H$ with benzoic acid or acetic acid **A2** proceeded to generate **208a** in improved yields of 35% and 29% yield (Table 11, entries 1–2). Other benzoic and aliphatic acids were trialled (*e.g.* 4-$NMe_2C_6H_4CO_2H$, $AdCO_2H$, pivalic acid, hexanoic acid) but none offered a further improvement. As discussed in Section 1.3.1, $(E)\text{-}(CHCOOMe)_2$ was found to be a beneficial additive in the (3+1+2) cycloaddition of aminocyclopropanes with tethered alkenes.[17] Consequently, it was reasoned that an electron-deficient ligand and/or acid additive could be advantageous in both (1) accelerating C–C reductive elimination and (2) inhibiting β-hydride elimination and hence improve the yield of **208a**.[166] With this hypothesis in mind, $(E)\text{-}(CHCOOMe)_2$ was assessed but was found to be completely ineffective (Table 11, entry 3). Gratifyingly however, the use of $(E)\text{-}(CHCOOH)_2$ delivered the target molecule **208a** in 44% isolated yield and with good selectivity over unsaturated variant **205a** (Table 10, entry 4, **208a**:**205a** = 9.0:1). When $(E)\text{-}(CHCOOMe)_2$ and $(E)\text{-}(CHCOOH)_2$ were used in combination,

the yield of product **208a** was not improved (Table 10, entry 5). Conversely, an increase in the loading of $[Rh(cod)OMe]_2$ and (*E*)-$(CHCOOH)_2$ resulted in an increase in yield of **208a** to 50% (Table 11, entry 6). Finally, running the reaction at 1.0 M afforded the target saturated molecule **208a** in 61% yield and with excellent selectivity over unsaturated **205a** (Table 11, entry 7, **208a**:**205a** = 15.0:1). Further variation of reaction parameters did not improve the yield of **208a**, therefore optimisation studies of this challenging substrate were concluded. Overall, the key changes *vs*. second generation conditions were the omission of $P(4\text{-}FC_6H_4)_3$ and the replacement of $2\text{-}NO_2C_6H_4CO_2H$ with (*E*)-$(CHCOOH)_2$.



Entry	X (mol%)	Additive	Y (mol%)	Conc.	Remaining 202a[a]	Yield 208a[a]	Yield 205a[a]	208a:205a
1	3.75	A1	150	0.67 M	52%	35%	-	1.0:0
2	3.75	A2	150	0.67 M	-	29%	11%	3.0:1
3	3.75	A3	75	0.67 M	80%	-	-	n.d.
4	3.75	A4	75	0.67 M	11%	44%[b]	<5%	9.0:1
5	3.75	A3 + A4	100[c]	0.67 M	-	40%	8%	5.0:1
6	5.00	A4	100	0.67 M	-	50%	10%	5.0:1
7	**5.00**	**A4**	**100**	**1.0 M**	**<5%**	**61%**[b]	**4%**	**15.0:1**

Table 11: Evaluation of different additives in the Rh(I)-catalysed carbonylative cyclisation of challenging substrate cyclopropylamide ***trans*-202a**.[d] The ratio of **208a**:**205a** was determined by ^1H NMR analysis of crude material. [a] Yields were determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [b] Isolated yield. [c] 100 mol% of (*E*)-$(CHCOOMe)_2$ and (*E*)-$(CHCOOH)_2$ were used. [d] Results obtained by G.-W. Wang.

2.7.4 Evaluation of third generation reaction conditions

With the $[Rh(cod)OMe]_2$/(*E*)-$(CHCOOH)_2$ catalytic system providing efficient access to the C7/8 saturated heterocycle, the scope with respect to substitution on the cyclopropane ring was examined (Table 12A). Pleasingly, these new conditions extended to more sterically demanding systems, such as cyclopropylamide ***trans*-202b**, which cyclised to provide heterocycle **208b** in 50% yield. Importantly, heterocyclisation of enantiopure *trans*-cyclopropylamide **(*S,S*)-202c** proceeded with retention of the R^3-substituted stereocentre to form heterocycle **208c** in 50% yield and with good e.r. (98.5:1.5 e.r.). The

new conditions also extended to substrates with different aromatic nucleophiles, as demonstrated by the formation of pyrrole **208d** in 48% yield. Likewise, a regiochemically distinct cyclisation *via* the C2 position of the heteroarene afforded pyrrole **208e** in 31% yield. However, at the present level of development, cyclisation of *cis*-1,2-disubstituted cyclopropylamide ***cis*-202a** delivered no product and unreacted starting material was recovered.

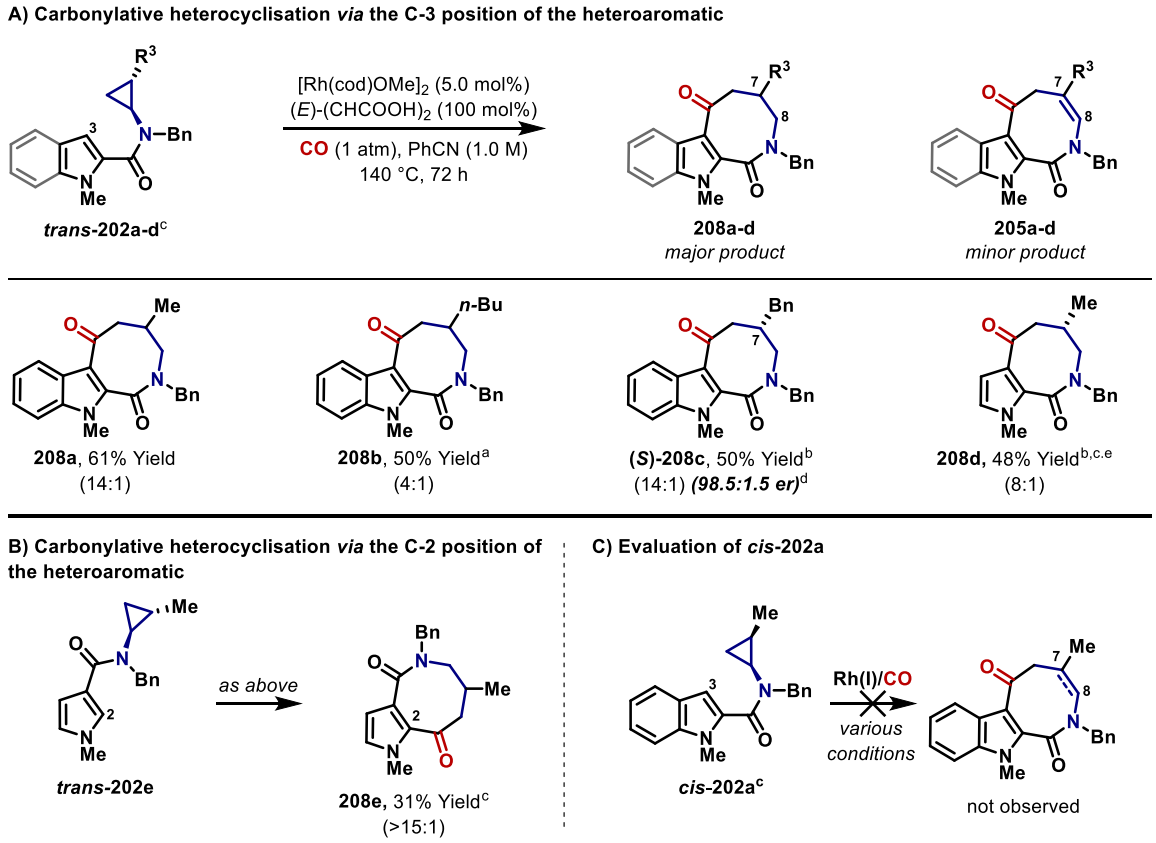
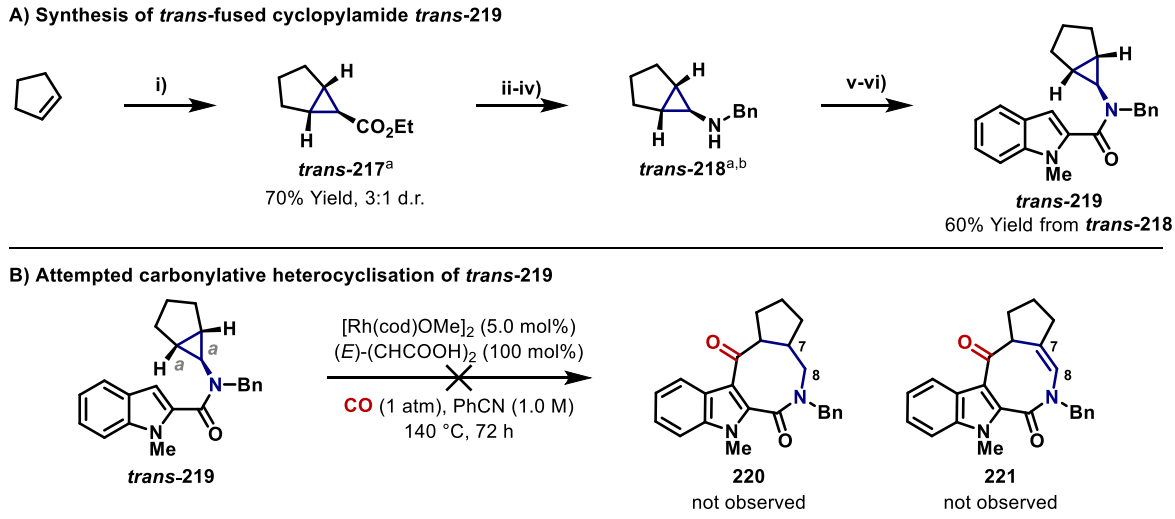


Table 12: Scope of *trans*- and *cis*-1,2-disubstituted cyclopropylamides. The ratio of **208a-e:205a-e** was determined by ^{1}H NMR analysis and is given in parentheses. The isolated yields for **208b**, **208d**, **208e** include **205b**, **205d**, **205e** [a] The reaction time was 120 h. [b] (*E*)-(CHOOH)$_2$ (150 mol%) was used in PhCN (0.67 M). [c] ***trans*-202d**, ***cis*-202a**, **208d** and **208e** were synthesised by G.-W. Wang. [d] From **(*S,S*)-202c** (98.5:1.5 e.r.). [e] The reaction temperature was 150 °C.

2.7.5 Fused cyclopropylamides

Having successfully demonstrated the compatibility of *trans*-1,2-disubstituted aminocyclopropanes, attention turned to evaluate trisubstituted aminocyclopropanes. Of particular interest was fused cyclopropane ***trans*-219** because, if compatible in the protocol, it would provide access to polyheterocyclic architectures (Scheme 58). Also note that the proximal C–C bonds of ***trans*-219** (*bond **a*** in ***trans*-219**) are chemically identical, which consequently eliminates the issue of regioselectivity in the C–C bond activation step. The synthesis of fused cyclopropane ***trans*-219** commenced with Rh(II)-catalysed cycloaddition between ethyl diazoacetate and cyclopentene to give cyclopropane

***trans*-217** in 70% yield and 3:1 d.r. Cyclopropane ***trans*-217** was then advanced to substrate ***trans*-219** using the same synthetic sequence utilised for aminocyclopropanes ***trans*-202a**–**e**. (*cf.* Scheme 55). With ***trans*-219** in hand, it was subjected to the third generation $[Rh(cod)OMe]_2$/(*E*)-$(CHCOOH)_2$ catalyst system. Disappointingly, ***trans*-219** failed to deliver the target heterocycles **220**/**221** and non-specific degradation of ***trans*-219** occurred. Similarly, the first and second generation conditions (as outlined in Table 2 entry 12 and Table 6, entry 14) were also ineffective. It was reasoned that the failure of ***trans*-219** to cyclise was due to the developing steric clash between the Rh-centre and the fused-cyclopentane ring during the C–C reductive elimination step. No further investigations into the carbonylative cyclisation of this challenging substrate were conducted.

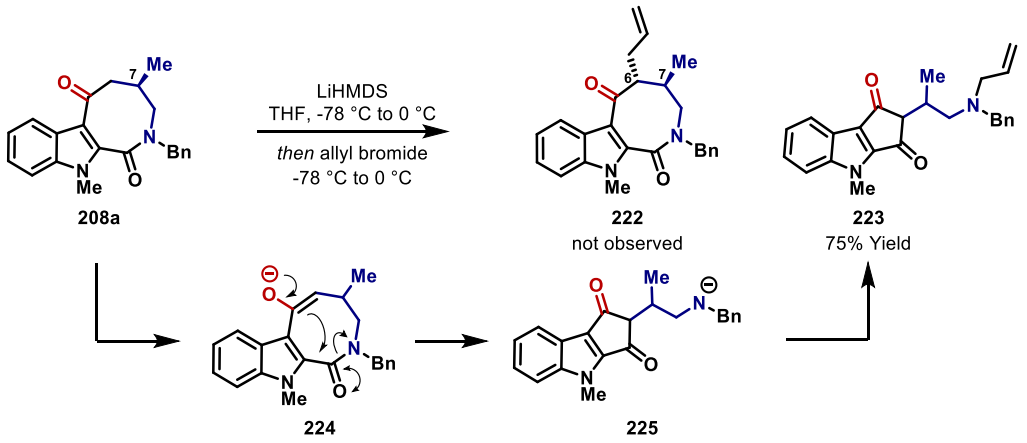


Scheme 58: Attempted Rh(I)-catalysed heterocyclisation of fused cyclopropylamide ***trans*-219.** A) *Reagnets and conditions*: i) ethyl diazoacetate, cat. $Rh_2(OAc)_4$, CH_2Cl_2, r.t., 16 h; ii) 4 M aq. NaOH, MeOH, r.t., 18 h; iii) diphenylphosphoryl azide, Et_3N, *t*-BuOH, 80 °C, 18 h; iv) TFA, CH_2Cl_2, r.t., 2 h *then* benzaldehyde, $NaHCO_3$, MeOH, reflux, 3 h *then* $NaBH_4$, 0 °C to r.t., 18 h; v) indole-1*H*-2-carboxylic acid, EDCI, DMAP (10 mol%), CH_2Cl_2, r.t. 6 h; vi) MeI, NaH (60% dispersion in oil), DMF, r.t., 2 h. [a] Synthesised by G.-W. Wang. [b] The *trans*- and *cis*-diastereomers were separated by flash column chromatography.

2.7.6 Product Derivatisation

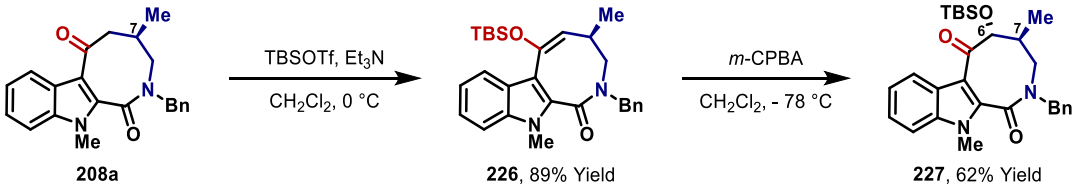
In the above investigations, it has been demonstrated that carbonylative heterocyclisations involving *trans*-1,2-disubstituted cyclopropylamides proceed with high selectivity for C-7 substituted heterocycles **208a**–**e**. It was therefore thought that substituents at the C-6 position (*i.e.* **213'**) could be introduced using enolate chemistry. To investigate the feasibility of this strategy, heterocycle **208a** was subjected to derivatisation. Surprisingly, treatment of **208a** with LiHMDS, followed by the addition of allyl bromide delivered 5-membered heterocycle **223** instead of the desired α-functionalised ketone **222** (Scheme 59). Presumably formation of **223** occurs *via* intramolecular attack of enolate **224** onto the lactam unit to give intermediate **225**, which is then *N*-alkylated to afford **223**. This undesired reaction outcome reinforces the propensity of the highly stained 8-membered ring to undergo ring contraction.

No attempt was made to avoid this deleterious reaction pathway by either an *in situ* quench or employment of an alternative base.



Scheme 59: Derivatisation of indole **208a**. Product **223** was synthesised by G.-W. Wang.

Alternatively, utilising a soft enolisation approach, ketone **208a** was readily converted to silyl enol ether **226**, which was then treated with *m*-CPBA to furnish α-functionalised product **227** as a single diastereomer in 62% yield (Scheme 60). The relative *trans* diastereorelationship of the C-7 methyl substituent to the C-6 OTBS group was confirmed by nOe experiments.



Scheme 60: Derivatisation of indole **208a**.

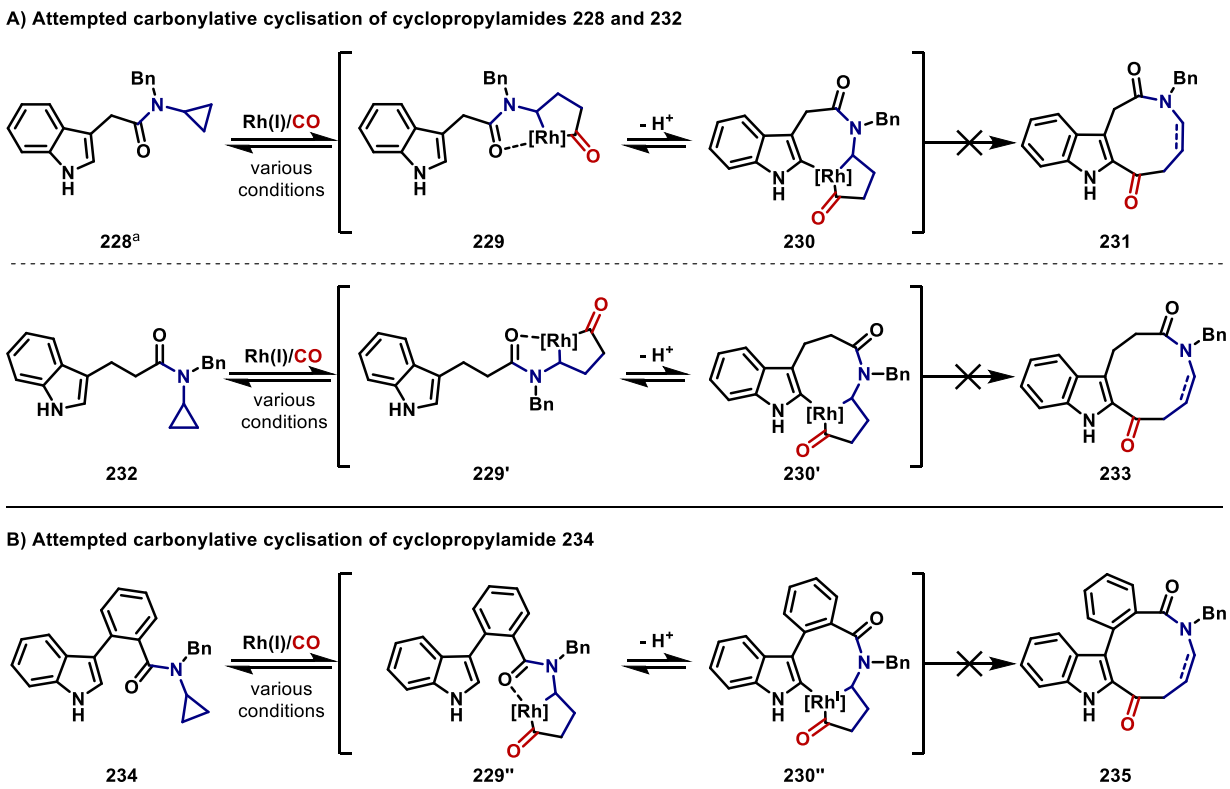
2.7 Future Directions

The studies discussed in this chapter have provided efficient access to heteroarene-annulated 8-membered *N*-heterocycles. In principal, the fundamental mechanistic steps involved (see Scheme 40) and the metallabicyclic templating effect could be exploited to form medium rings of other sizes (*i.e.* 9–11 membered rings). Furthermore, the discovery that non-carbonylative 7-membered heterocycle **181** was formed when 1,2-DCB was used as the reaction solvent presented an opportunity to develop non-carbonylative ring expansions of aminocyclopropanes. In the following section, preliminary investigations towards both these goals are outlined.

2.7.1 The search for larger ring systems

Initially, efforts were directed towards synthesising more challenging 9- and 10-membered indole-fused *N*-heterocycles. To this end, substrates **228** and **232**, possessing methylene spacers between the indole

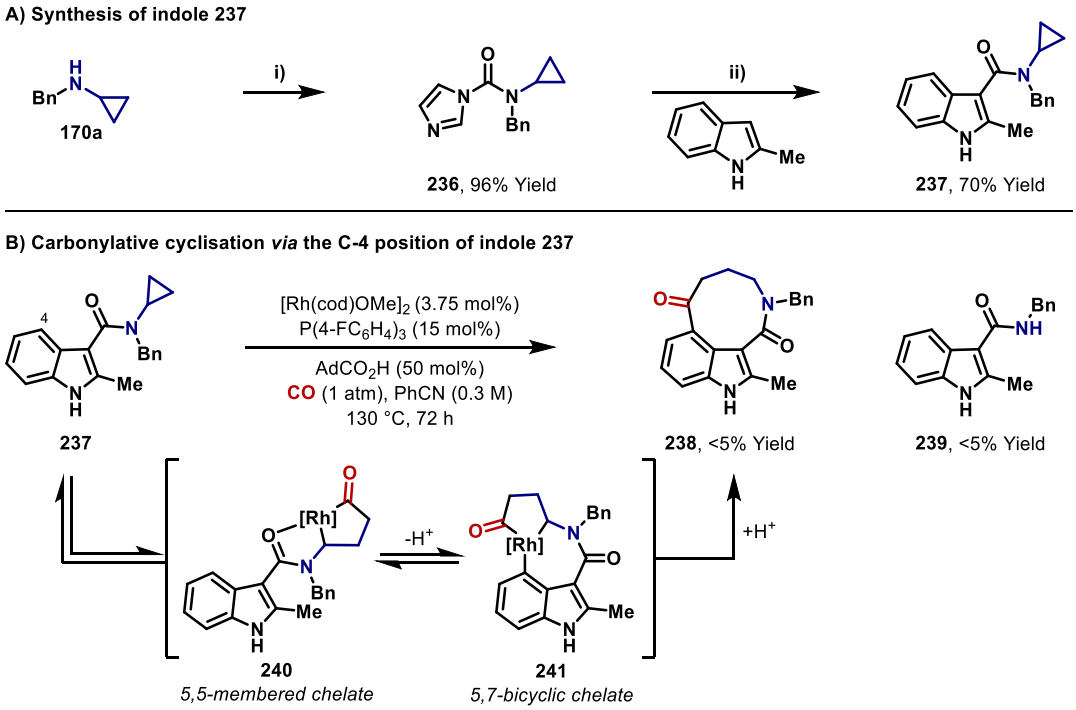
C-3 position and the cyclopropylamide unit, were subjected to the carbonylative cyclisation protocol (Scheme 61A). However, target products **231**/**233** were not detected and the majority of the mass balance consisted of unreacted **228**/**232**. Other conditions were tested (e.g. alternative Rh(I) pre-catalysts, phosphine ligands, range of acid additives), but in all cases no desired product was obtained. It was proposed that the lack of reactivity exhibited by indoles **228** and **232** was due to two factors. Firstly, in accordance with previous studies (see Section 2.6), rhodacyclopentanone formation (*i.e.* **229** or **229'**) and subsequent C(sp^2)–H metallation are reversible; consequently, on the basis of ring size, equilibrium favours the 5,5-membered chelate **229**/**229'** over the 7,5-Rh(III)-chelate **230** *or* 8,5-Rh(III)-chelate **230'**. This preference thereby hinders access to key metallabicycles **230**/**230'** and hence prevents the C–C reductive elimination step from occurring. Secondly, substrates **228** and **232** possess a high degree of conformation flexibility which likely imposes an additional kinetic barrier to cyclisation. To circumvent these issues, substrate **234** was designed which possesses a conformationally rigid phenyl linker; however, indole **234** was not compatible under a variety of Rh(I)-catalysis conditions and non-specific degradation of **234** was observed in each case (Scheme 61B).



Scheme 61: Attempted Rh(I)-catalysed carbonylative cyclisation of cyclopropylamides to form 9- and 10-membered *N*-heterocycles. [a] Substrate **228** was synthesised by G.-W. Wang.

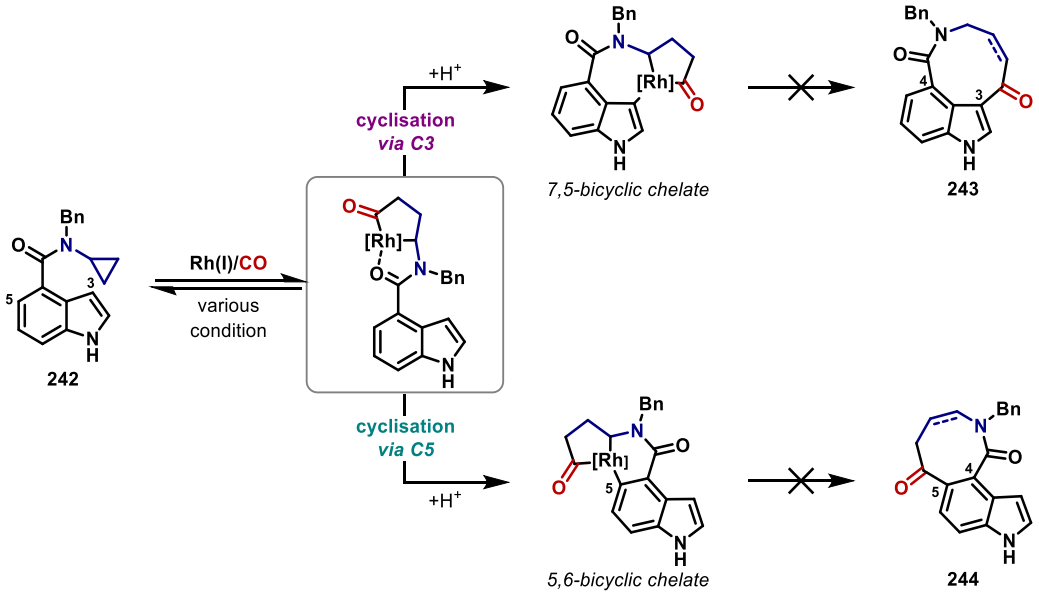
As discussed in Section 2.6, pyrrole **186a** could be induced to cyclise *via* C-4 by pre-installing a methyl blocking group at the C-2 position (see Scheme 50). Encouraged by the effectiveness of this strategy, we questioned whether a similar tactic could be utilised to promote cyclisation *via* the

benzenoid ring of a tailored indole substrate. Methodologies that enable site-selective functionalisation of the benzenoid ring of indole remain a formidable challenge due to the inherent reactivity of the C-2 and C-3 positions.[167-169] However, recent advances in transition-metal catalysis have emerged to achieve C-4 functionalisation of indole scaffolds and, in the majority of cases, site-selectivity is achieved by using a C-3 directing group.[169-171] To test the viability of this strategy, C-4 carbamoyl indole **237**, possessing a C-2 methyl group, was synthesised in a two-step sequence (Scheme 62A). Following a known procedure, acylation of aminocyclopropane **170a** with 1,1′-carbonyldiimidazole afforded **236** in 96% yield, which was then converted to indole **237** by $AlMe_3$ mediated Friedel-Crafts carbamoylation of 2-methylindole.[172] Exposure of indole **237** to $[Rh(cod)OMe]_2/AdCO_2H$ carbonylative catalysis conditions led to a <5% yield of C3-4 annulated product **238**. Unfortunately, purification of **238** was difficult due to the formation and co-elution of side-product **239**. Side-product **239** presumably forms *via* hydrolysis of the corresponding enamide, which is generated by degradation of the rhodacyclopentanone intermediate **240**. Note that structural assignment of indole **238** is tentative, but is supported by characteristic ^1H NMR signals and mass spectrometry data. For the same aforementioned reasons, it was proposed that access to the critical 5,7-Rh(III)-chelate **241** is disfavoured and C–C reductive elimination from **241** is highly challenging due to the innate strain of the 9-membered ring being formed. Alternative reaction conditions were evaluated, but no improvement could be made and hence investigations into this transformation were stopped.



Scheme 62: *Reagents and conditions*: i) 1,1′-carbonyldiimidazole, THF, reflux, 16 h, 96%; ii) 2-methylindole, $AlMe_3$ (2.0 M in PhMe), PhMe, 0 °C, 45 minutes *then* 105 °C, 4 hours, 70%.

Following a similar line of thought, C-4 carbamoyl indole **242** was prepared and subjected to the $[Rh(cod)OMe]_2$/$P(4\text{-}FC_6H_4)_3$/$2\text{-}NO_2C_6H_4CO_2H$ catalyst system. It was envisaged that indole **242** would either undergo cyclisation *via* the C-3 position to afford the 9-membered heterocycle **243** or *via* the C-5 position to afford the 8-membered heterocycle **244** (Scheme 63). On the basis of intrinsic nucleophilicity of the indole core, the former pathway was deemed more likely. However, indole **242** was extremely resilient to C–C bond activation, even at an elevated temperature of 150 °C, and neither heterocycles **243**/**244** were observed.



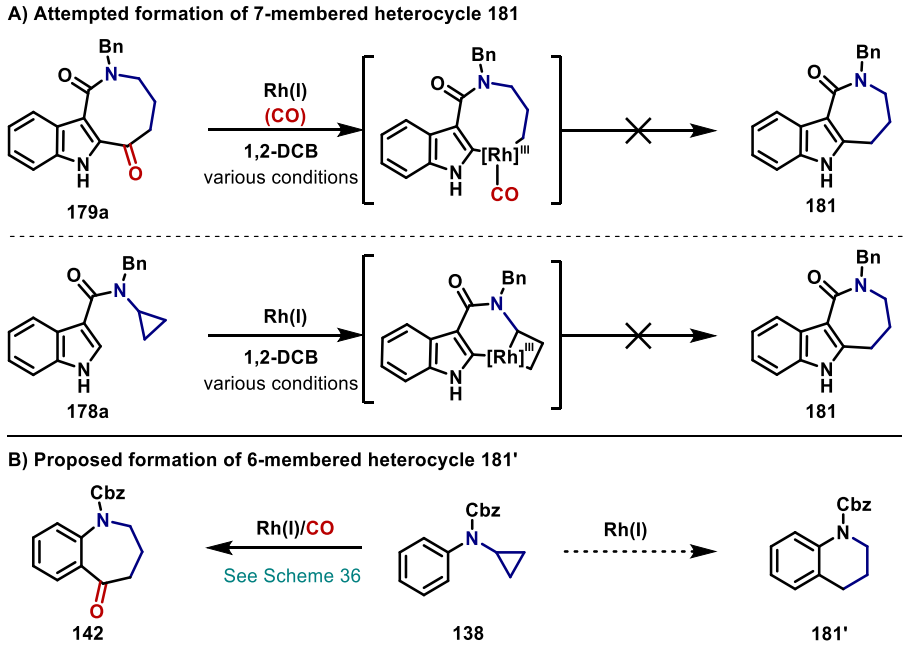
Scheme 63: Attempted Rh(I)-catalysed carbonylation of C-4 carbamoyl indole **242**.

At this point, all investigations to generate 9- and 10-membered heterocyclic products were halted. It was concluded that for such ambitious targets, the kinetic barrier to cyclisation becomes prohibitively high (due to the increased size of the requisite 5,7-Rh(III)-bicyclic intermediate) and the entropic price for achieving an organised Rh(III)-chelate cannot be repaid by the release of cyclopropane ring strain. Consequently, the overall reaction pathway is not sufficiently exergonic to compensate for the ring strain of the final heterocyclic product.

2.7.2 The search for a protocol involving non-carbonylative C–C bond activation of aminocyclopropanes

The development of a protocol enabling the non-carbonylative ring expansions of aminocyclopropanes is an attractive extension of this work and, more importantly, has not been demonstrated previously. As shown in Scheme 47, it was hypothesised that mechanistically heterocycle **181** was formed either *via* decarbonylation of 8-membered heterocycle **179a** or *via* a rhodacyclobutane-based pathway. To test the possibility of the former pathway, a sample of pure heterocycle **179a** was subjected to identical catalytic conditions in 1,2-DCB (either with or without an atmosphere of CO, Scheme 64A). However, from

these experiments, the 7-membered ring product **181** was not observed and the starting material was recovered entirely. This would seemingly rule out a pathway involving decarbonylation of the 8-membered product **179a**.[69] To test the likelihood of the latter proposal, indole **178a** was exposed to the $[Rh(cod)OMe]_2$/1,2-DCB system in the *absence* of CO (Scheme 64A). However, **181** was not detected, thus indicating that CO is required for its generation. Nevertheless, this pathway cannot be discounted as the role of CO could simply be to act as a π-acceptor ligand. It is worth noting that replacement of $[Rh(cod)OMe]_2$ with $[Rh(CO)_2Cl]_2$ was also ineffective. Due to other successful research avenues, no further investigations into the formation of 7-membered heterocycle **181** was pursued at this time. It is conceivable that non-carbonylative ring expansion of aminocyclopropanes might be better suited for the synthesis of 6-membered rings compared to 7-membered adducts. Thus, future studies will target the design of a 6-membered variant and an obvious starting point would be to examine the non-carbonylative ring expansion of aminocyclopropane **138** (Scheme 64B).



Scheme 64: Preliminary studies to identify a protocol involving non-carbonylative C–C bond activation of aminocyclopropanes

2.8 Summary and Conclusion from the studies in Chapter 2

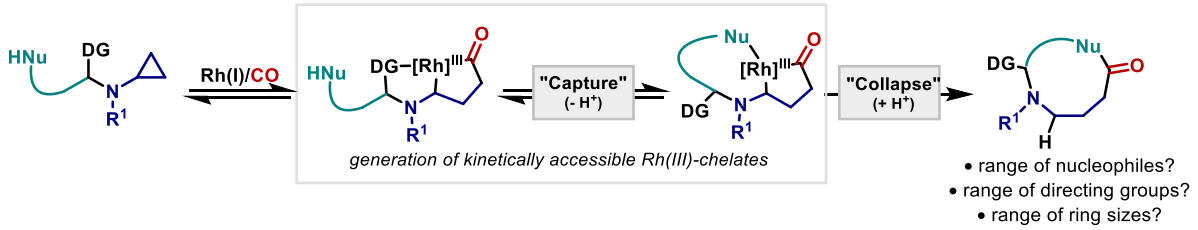
In summary, the first Rh(I)-catalysed "capture-collapse" heterocyclisation that provides heteroarene annulated 8-membered rings has been developed. The central paradigm of this approach relies upon the tandem exploitation of cyclopropane strain relief and metallabicycle templating to overcome the usual entropic barriers associated with medium-sized ring closures. The protocol is highly flexible with regards to both the nature and position of the heteroaromatic unit, and affords ring systems that are difficult to construct using conventional methods. Extensive and thorough optimisation of reaction

conditions was required to facilitate the formation of saturated, sp^3-rich, heterocycles **152**/**179**/**208** as the major product. Evidence gained through deuterium labelling experiments support reversible rhodacyclopentanone formation *via* carbonylative C–C bond activation and C–H metallation (see Schemes 52 and 53). Further studies are needed to extend the methodology to systems with electron-neutral/poor aromatic units and systems that generate other challenging medium ring sizes (*i.e.* ≥8-membered).

Chapter 3 – Further investigations into the nucleophilic trapping of rhodacyclopentanones

3.1 Introduction

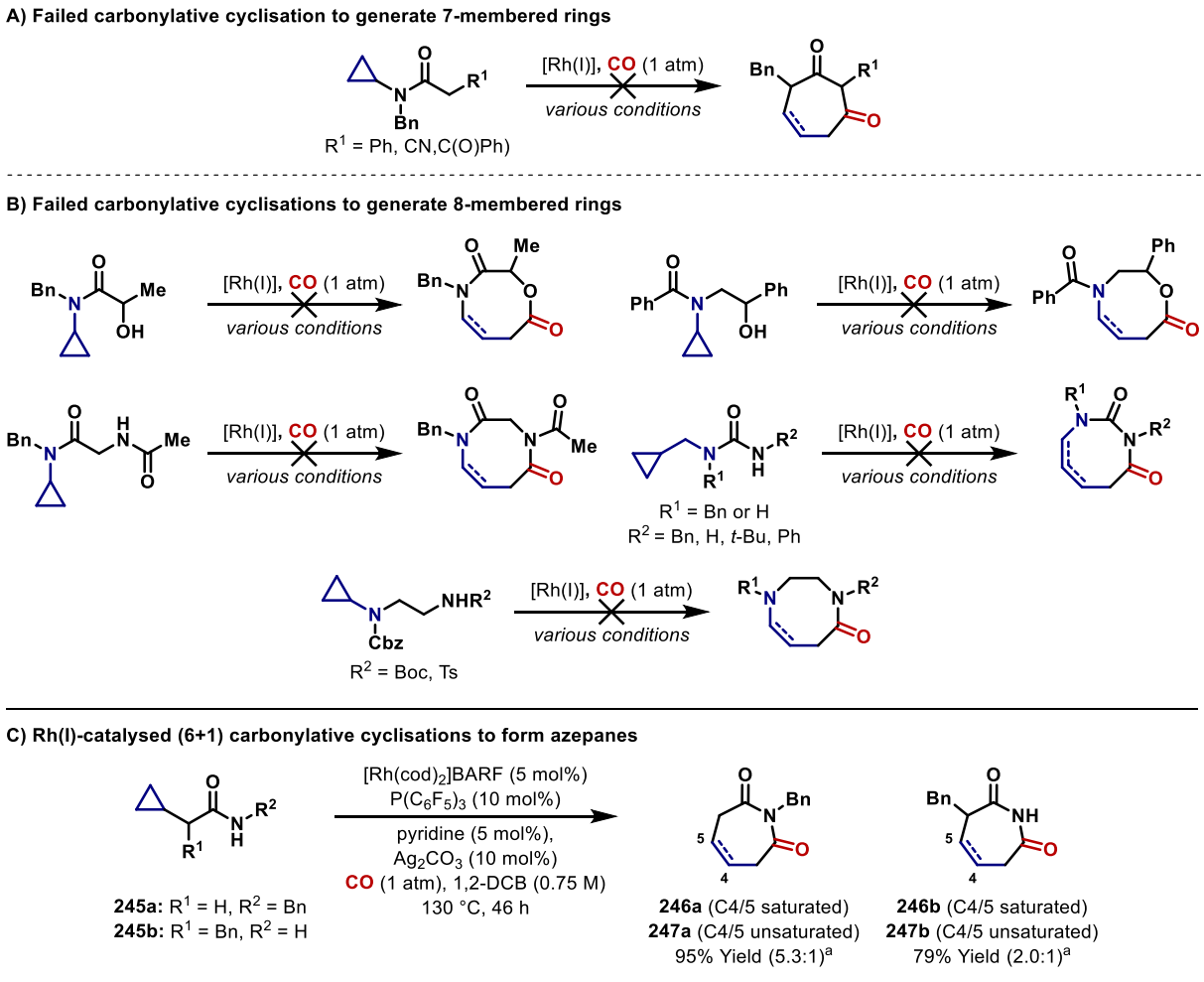
In Chapter 2 it was demonstrated that Rh(I)-catalysed "capture-collapse" heterocyclisations could be extended to 8-membered *N*-heterocycles *via* the trapping of rhodacyclopentanones with tethered C-based heteroarene nucleophiles. Given the intrinsic electrophilicity of rhodacyclopentanones, it was envisaged that variation of the directing group and the nucleophilic component might provide entry to related *N*-heterocyclic structures (Scheme 65). With this goal in mind, investigations were undertaken to evaluate and identify a second intramolecular protocol.



Scheme 65: Mechanistic blueprint for the identification of related "capture-collapse" processes.

3.1.1 Previous studies conducted in the Bower group

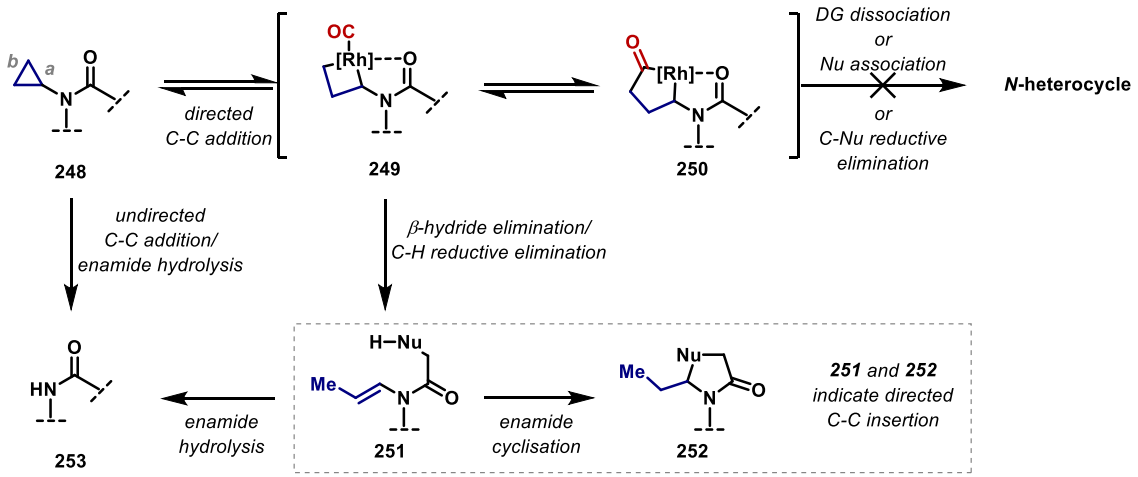
Before discussing efforts to extend the "capture-collapse" methodology, it is pertinent to highlight previous research undertaken in the Bower group in related Rh(I)-catalysed heterocyclisations (Scheme 66). Former PhD students N. McCreanor and S. Stanton investigated several systems to target 7- and 8-membered *N*-heterocycles *via* the intramolecular trapping of rhodacyclopentanones with tethered N-, C- and O-based nucleophiles (*e.g.* amines, amides, enolates and alcohols)[96,102] Efforts involving aminocyclopropane substrates with a pendant alcohol, amine or enolate nucleophilic component were unsuccessful (Scheme 66A-B); however, S. Stanton discovered that cyclopropylmethylamides **245a**–**b** underwent Rh(I)-catalysed carbonylative cyclisation to form azepanes **246a**–**b** in high yield, but with poor control over the oxidation level of the C4/C5 position (*e.g.* **246a** was formed in 95% yield with 5.3:1 selectivity over **247a**) (Scheme 66C).[102] Preliminary optimisation studies revealed that pyridine and Ag(I)-salts were beneficial additives; however, their precise role remained unclear.



Scheme 66: Previous Rh(I)-catalysed "capture-collapse" heterocyclisations investigated in the Bower group. [a] The ratio of **246a**–**b**:**247a**–**b** was determined by ^{1}H NMR analysis of crude material and is given in parentheses.

Several common side-products were observed during these investigations, which provided important information on competing side-reactions (Scheme 67). For example, several of the substrates depicted in Scheme 66 formed a mixture of linear alkenes **251**, cycloadducts **252** or protodecyclopropanated starting material **253** when exposed to Rh(I)-catalysed carbonylative conditions. Linear alkenes **251** are formed by Rh(I)-addition to the more hindered (*bond **a***) cyclopropyl C–C bond of **248** (**248** to **249**), followed by β-hydride elimination and C–H reductive elimination. Cycloadducts **252** likely arise *via* reaction of the nucleophilic unit with the enamide of **251**. Conversely, protodecyclopropanated products **253** are formed by Rh(I)-addition to either *bond **a** or bond **b*** of **248**, followed by β-hydride elimination, C–H reductive elimination and hydrolysis of the resulting enamide. The formation of alkenes **251** (and/or adducts **252**) is considered indirect proof that the desired rhodacyclopentanone **250** has formed. It is assumed that inefficient trapping of this species allows reversal to rhodacyclobutane **249**, which ultimately results in undesired side-reactions. The problematic steps of these processes could be either directing-group dissociation, nucleophile association, nucleophilic deprotonation or C–Nuc reductive elimination. In contrast, the formation of

protodecyclopropanated side-products **253** are not considered proof of directed Rh(I)-addition as they can arise *via* oxidative addition of either *bond* ***a*** or *bond* ***b*** of cyclopropane **248**.



Scheme 67: Common side-products identified from failed Rh(I)-catalysed carbonylative heterocyclisations.

3.2 The search for a second intramolecular protocol

To illustrate further the synthetic utility of the Rh(I)-catalysed "capture-collapse" heterocyclisations, several cyclopropane-based substrates were designed and evaluated. As the catalytic requirements for each substrate class were unknown, each substrate was evaluated under representative carbonylative conditions, which included a cationic or neutral Rh(I)-source, phosphine ligand, benzoic acid additive and either PhCN or 1,2-DCB as the reaction solvent.

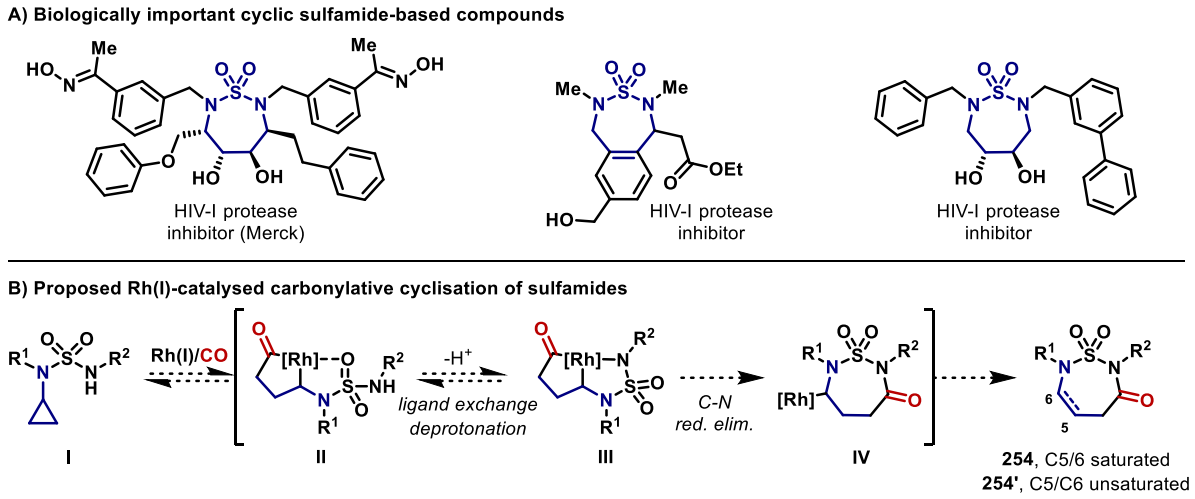
3.2.1 Studies towards the synthesis of 7-membered N-heterocycles

Note the work carried out in this section was conducted prior to the studies outlined in Chapter 2

3.2.1.1 Design and evaluation of cyclopropyl sulfamides

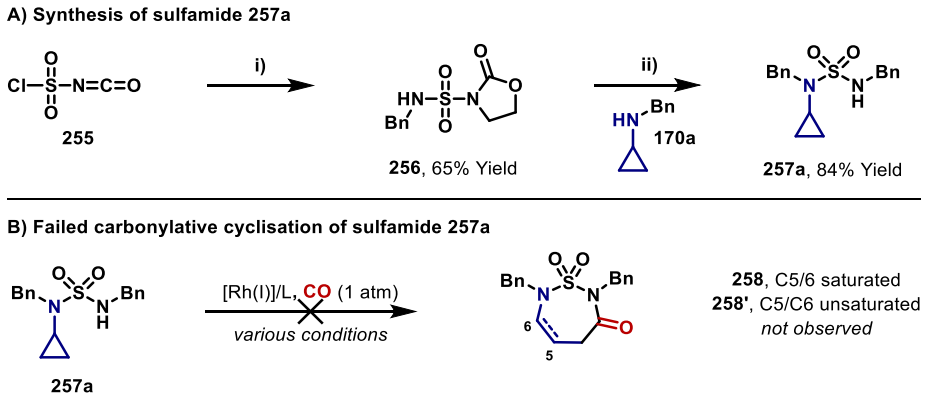
As discussed previously in Chapter 2, heterocyclic 7- and 8-membered rings are ubiquitous structural features in many natural products and pharmaceutical agents (see Section 2.2). Among these scaffolds, 7-membered cyclic sulfamides have emerged as attractive peptidomimetics in the design of HIV-I protease inhibitors (Scheme 86A).[173-177] To date, the majority of transformations that generate 7-membered cyclosulfamide scaffolds can be divided into two reaction classifications: (i) intramolecular cyclisation of linear sulfamides *via* *N*-alkylation[178,179] or ring-closing metathesis[180,181] and (ii) direct incorporation of the sulfamoyl moiety by reacting sulfamide ($H_2NSO_2NH_2$) with diamines at elevated temperatures.[174,175] Given the relevance of these heterocycles, the development of a streamlined catalytic method for their construction would be of interest. With this in mind, it was envisaged that sulfamide **I** might direct insertion of a suitable Rh(I)-catalyst and carbon monoxide into the proximal cyclopropyl C–C bond to give rhodacyclopentanone **II** (Scheme 86B). From here, ligand

exchange with the nucleophile and concomitant deprotonation generates rhodacycle **III**, from which C–N reductive elimination to Rh(I)-alkyl intermediate **IV** secures the 7-membered ring. Finally, protodemetallation or β-hydride elimination would afford either saturated or unsaturated cyclic sulfamides **254**/**254'** respectively.



Scheme 68: Proposed Rh(I)-catalysed carbonylative heterocyclisation of cyclopropyl sulfamides to generate 7-membered cyclic sulfamides.

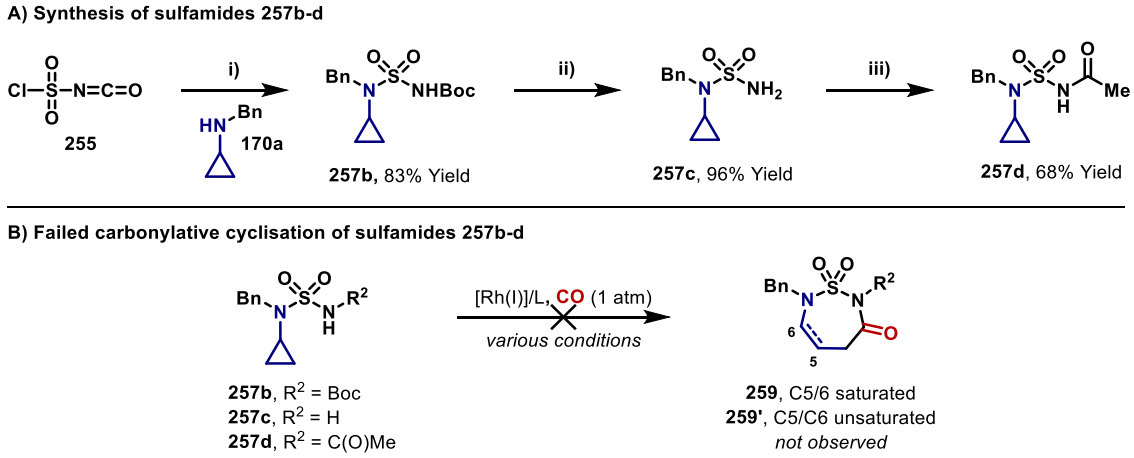
To reduce this idea to practice, trisubstituted cyclopropyl sulfamide **257a** was selected as an initial pilot substrate and, following a known procedure, was readily prepared in a 2-step sequence (Scheme 69A).[182,183] Sequential treatment of chlorosulfonyl isocyanate **255** with 2-chloroethanol and benzylamine provided *N*-sulfamoyloxazolidinone **256** in 65% yield. Subsequent displacement of the oxozolidinone ring of **256** by amine **170a** afforded sulfamide **257a** in 84% yield.



Scheme 69: Preparation and evaluation of sulfamide **257a**. *Reagents and Conditions*: i) 2-chloroethanol, CH_2Cl_2, 0 °C to r.t. *then* Et_3N *and* benzylamine, CH_2Cl_2, 0 °C to r.t. 65%; ii) amine **170a**, Et_3N, MeCN, reflux, 84%.

With substrate **257a** in hand, it was exposed to representative carbonylative conditions using a range of Rh(I)-sources in combination with mono-/bidentate phosphine ligands in 1,2-DCB. Disappointingly, all attempts to effect carbonylative cyclisation of sulfamide **257a** failed, and instead, nonspecific degradation of **257a** was observed in every case by ^{1}H NMR analysis of the crude reaction mixtures (Scheme 69B).

Undeterred by this set-back, it was reasoned that modulation of the R^2 substituent of sulfamide **I** might influence the acidity of the N–H bond and make it more amenable to nucleophilic addition to rhodacyclopentanone **III**, which, in turn, might aid cyclisation. To test this hypothesis, cyclopropyl sulfamides **257b**–**d** bearing different R^2 substituents were prepared (Scheme 70A). *N*-Boc derivative **257b** was accessed by successive treatment of chlorosulfonyl isocyanate **255** with *tert*-butyl alcohol and benzylcyclopropyl amine **170a** in 83% yield. TFA-mediated Boc-deprotection of **257b** delivered *N*-*N'*-disubstituted cyclopropylsulfamide **257c** in 96% yield, and *N*-acetyl substrate **257c** was formed in 68% yield by coupling of **257c** with acetyl chloride. Cyclopropyl sulfamides **257b**–**d** were then exposed to a range of carbonylative conditions; unfortunately, formation of cyclic sulfamides **259**/**259'** were not observed in any case and sulfamides **257b**–**d** either decomposed or remained unreacted (Scheme 70B). In light of these difficulties, investigations into the cyclisation of sulfamides were halted in favour of alternative systems. In order to assess the viability of a sulfamide directing group, it would be insightful to conduct oxidation insertion studies with sulfamides **257a**–**d** (*cf.* Scheme 25); however, these experiments were not investigated at this stage.

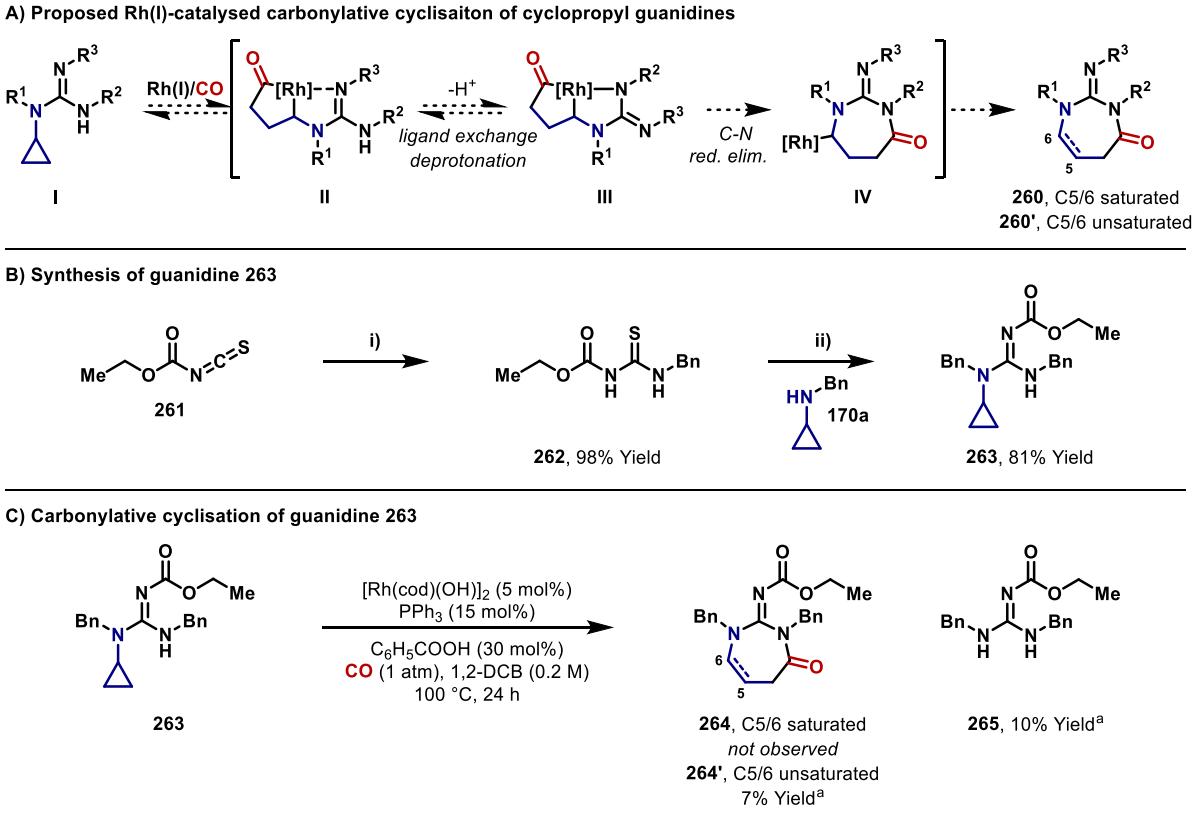


Scheme 70: Preparation and evaluation of sulfamides **257b-d**. *Reagents and Conditions*: i) *t*-BuOH, CH_2Cl_2, 0 °C to r.t., *then* Et_3N and amine **170a**, CH_2Cl_2, 0 °C to r.t. 83%; ii) TFA, CH_2Cl_2, 0 °C; iv) acetyl chloride, pyridine, CH_2Cl_2, r.t..

3.2.1.2 Design and evaluation of cyclopropyl guanidines

In subsequent studies, cyclopropyl guanidines **I** were evaluated as candidate substrates for Rh(I)-catalysed "capture-collapse" heterocyclisations (Scheme 71A). It was proposed that *N*-directed

C–C bond activation of **I** to rhodacyclopentanone **II**, followed by deprotonation and nucleophilic addition would provide rhodacycle **III**. From here, C–N reduction elimination and subsequent proto-demetallation or β-hydride elimination would deliver cyclic guanidines **260**/**260'** (Scheme 71A). As the requirements of the R^1, R^2 and R^3 substituents of guanidine **I** were unclear, trisubstituted guanidine **263** was selected as a trial substrate. Guanidine **263** was readily synthesised from isocyanate **261** following a simple 2-step protocol (Scheme 71B).[184] Treatment of isocyanate **261** with benzylamine afforded thiourea **262** in 98% yield. Next, EDCI-mediated coupling of **262** with amine **170a**, provided the desired cyclopropyl guanidine **263** in 81% yield.



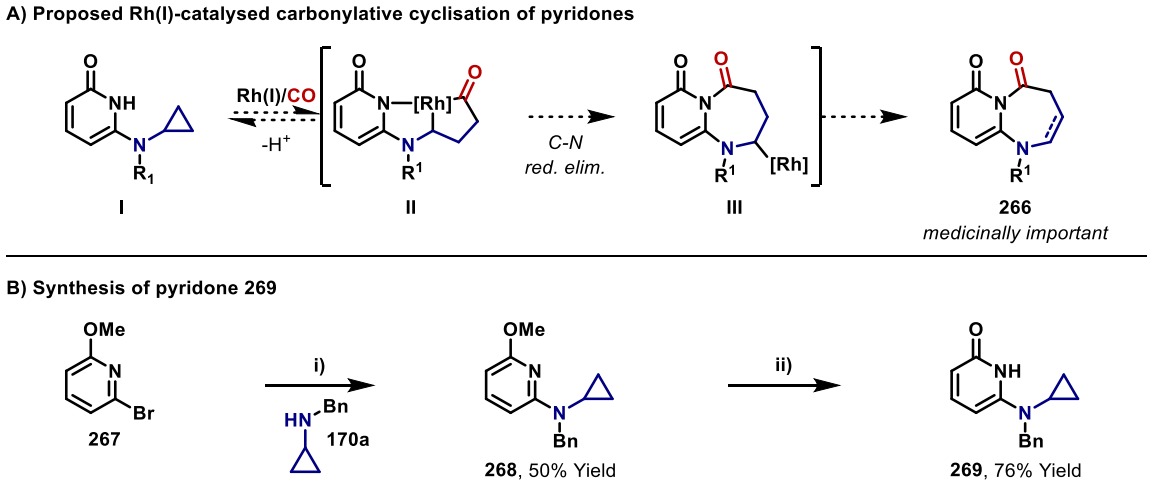
Scheme 71: B) *Reagents and conditions*: i) CH_2Cl_2, 0 °C to r.t., 98%; ii) EDCI, Et_3N, CH_2Cl_2, r.t., 81%. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

Exposure of guanidine **263** to [Rh(cod)OH]$_2$/1,2-DCB catalyst system led to a 7% yield of C5/C6 unsaturated 7-membered guanidine **264'** (Scheme 71C). Of note, the saturated analogue **264** was not observed by ^{1}H NMR analysis of the crude mixture. Unfortunately, the purification of **264'** was problematic due to the formation and co-elution of side-product **265**. As discussed above, protodecyclopropanated adducts akin to **265** can arise from degradation of the required rhodacyclopentanone intermediate (see Scheme 67). Note that the structural assignment of cyclic guanidine **264** is tentative, but is supported by characteristic ^{1}H NMR signals, mass spectrometry data and comparison to analogous products (*cf.* diazepane **120**). No further improvements could be made to

the yield of cyclic guanidine **264'**, and consequently, no further work was undertaken on this class of substrate.

3.2.1.3 Design and evaluation of cyclopropyl pyridones

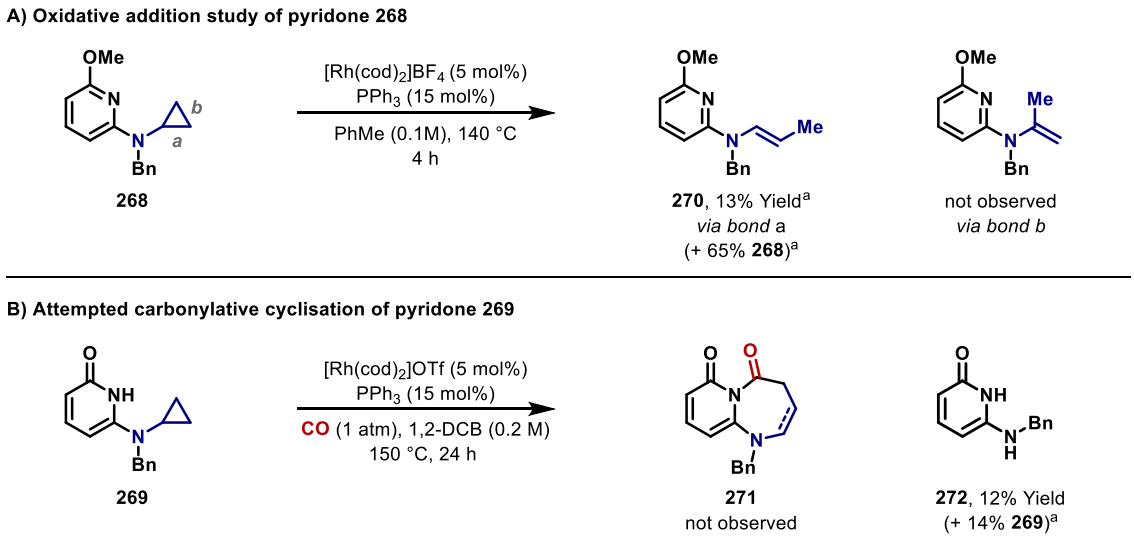
Bicyclic pyridones are important building blocks that are found in a wide range of natural products and pharmacologically active molecules. Among this class of compounds, 6,7-bicyclic pyridones (*e.g.* **266**, Scheme 72A) are present in several bioactive compounds, and this scaffold, or closely related variants, has been incorporated into the design of several analgesics and anti-inflammatory agents.[185] Generally, the 7-membered ring is assembled *via* intramolecular nucleophilic substitution or intramolecular condensation of 2,6-dihydropyridines.[185,186] To complement these approaches, it was proposed that *N*-directed C–C bond activation of cyclopropylpyridone **I** to rhodacyclopentanone **II**, followed by C–N reductive elimination to alkyl-Rh(I) intermediate **III**, and either protodemetallation or β-hydride elimination would form bicyclic pyridone **266** (Scheme 72A). In order to evaluate this hypothesis, cyclopropyl pyridone **269** was prepared as a test substrate (Scheme 72B). Buchwald-Hartwig cross-coupling between aryl bromide **267** and amine **170a** delivered pyridine intermediate **268** in 50% yield. Subsequent deprotection of the methoxy group with TMSCl/NaI afforded cyclopropyl pyridone **269** in 76% yield.



Scheme 72: B) *Reagents and conditions:* i) $Pd(OAc)_2$ (5 mol%), dppp (10 mol%), NaO*t*-Bu, PhMe, 80 °C, 14 h, 50%; ii) NaI, TMSCl, MeCN, 80 °C, 2 h *then* MeOH, r.t. 2 h, 76%.

Initially, to demonstrate the feasibility of *N*-directed oxidative addition, an insertion experiment was conducted on cyclopropyl pyridine **268** (Scheme 73A). It was found that, in the absence of CO, cyclopropyl pyridine **268** underwent directed Rh(I)-addition *via* insertion into the more hindered C–C bond (*bond* ***a***) to form linear alkene **270** in 13% yield. This result confirms that *N*-directed Rh(I)-addition is possible from a pyridine-based substrate and the observed regioselectivity is in agreement with previous reports (see Scheme 25). Encouraged by this result, it was anticipated that under carbonylative conditions, cyclopropyl pyridone **269** might behave in a similar manner and

tautomerize to its corresponding hydroxypyridine or, alternatively, undergo NH metallation prior to *N-directed* C–C bond activation. Either of these scenarios would enable access to the key 5,5-rhodacycle intermediate (*cf.* intermediate **II**, Scheme 72). With this hypothesis in mind, substrate **269** was subjected to carbonylative conditions using various Rh(I)-sources and mono-/bidentate phosphine ligands in either 1,2-DCB or PhCN. Unfortunately, **269** proved extremely resistant to C–C bond activation, and typically 80% recovered starting material was obtained. Increasing the reaction temperature to 150 °C led to the formation of protodecyclopropanated side-product **272** in 12% yield, but the desired product **271** was not observed (Scheme 73B). The formation of **272** indicates that C–C bond activation does occur, and as discussed above, this might indicate that pyridone **269** tautomerizes to its corresponding hydroxypyridine prior to C–C bond activation. In an attempt to facilitate deprotonation of the pyridone NH, several inorganic bases (*e.g.* K_2CO_3 and NaO*t*-Bu) were included; however, the inclusion of bases did not afford bicyclic heterocycle **271** and complete starting material recovery was observed. Consequently, after these initial studies, no further work was undertaken on this class of substrate.

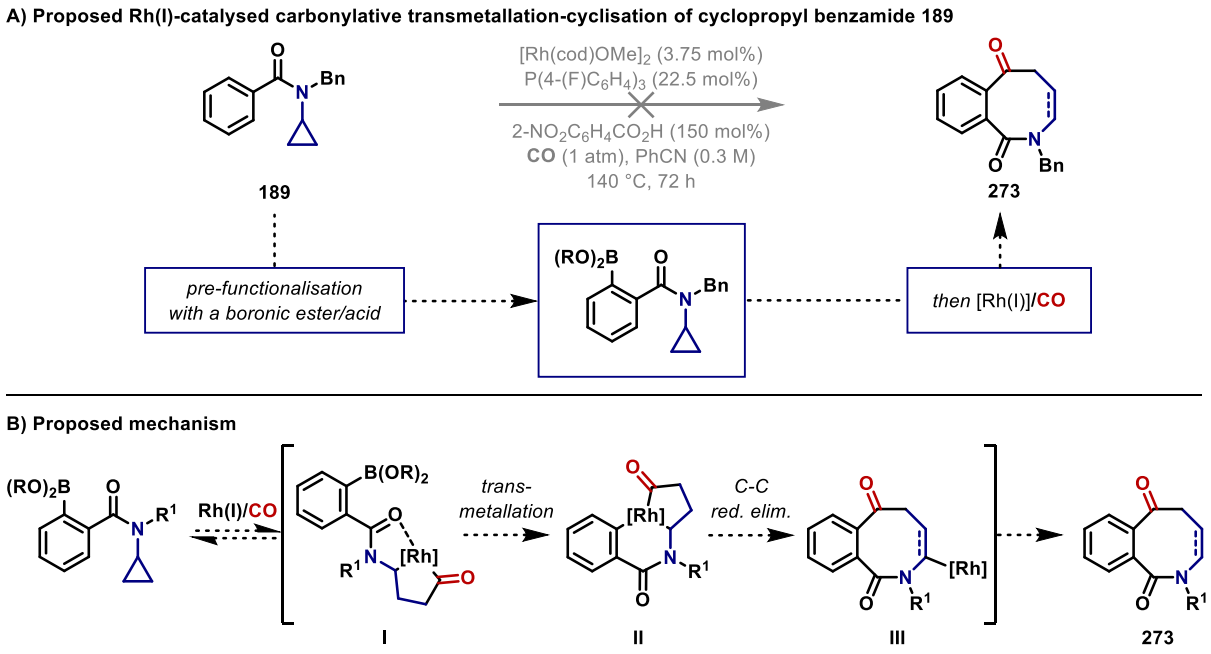


Scheme 73: [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

3.2.2 Studies towards the synthesis of 8-membered *N*-heterocycles *via* a Rh(I)-catalysed carbonylative transmetallation-heterocyclisation strategy

As outlined in Chapter 2, the Rh(I)-catalysed carbonylative cyclisation of cyclopropylamides to target 8-membered *N*-heterocycles was successfully realised. However, despite the robustness of this approach, the process was restricted to systems with electron-rich heteroaromatic units, which limits wider application of the methodology. In particular, phenyl-based system **189** was incompatible under the optimised conditions identified for indole-based system **178a**, and failed to deliver the target heterocycle (see Scheme 51 and Section 2.6). It was therefore hypothesised that pre-functionalisation

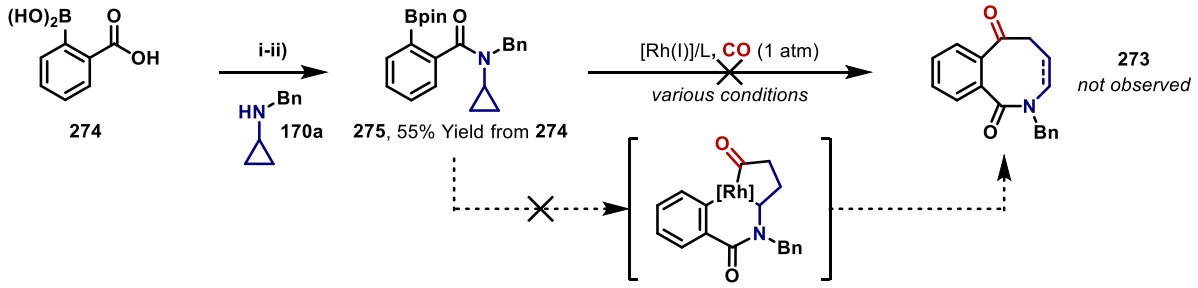
of the phenyl ring of **189** with a boronic acid/ester might promote trapping of the key rhodacyclopentanone intermediate *via* transmetallation (instead of *via* C–H metallation as detailed in Chapter 2) (Scheme 74). In this scenario, it was envisaged that carbonyl-directed rhodacyclopentanone formation to **I**, followed by transmetallation to 6,5-rhodacycle **II** and C–C reductive elimination would deliver alkyl Rh(I)-intermediate **III**. Finally, protodemetallation or β-hydride elimination would deliver benzofused azocine **273**. Alternatively, it is conceivable that transmetallation could occur first to give an aryl-Rh(I) intermediate,[187] from which subsequent C–C oxidative addition and CO insertion would allow alternative entry to 6,5-rhodacycle **II**. Whilst the use of pre-functionalised starting materials requires extra synthetic manipulations and reduces the atom economy of the process, the opportunity to access medicinally relevant benzoannulated 8-membered *N*-heterocycles is highly appealing. As discussed in Section 2.2, such molecular architectures are highly sought after in the pharmaceutical sector.[120] Additionally, in recent years, steady advances have been made to install boronic esters catalytically from simple arene precursors,[188-191] which could potentially allow straight-forward entry to the desired pre-functionalised aminocyclopropane substrate.



Scheme 74: Proposed extension to target 8-membered *N*-heterocycles *via* a Rh(I)-catalysed carbonylative transmetallation-heterocyclisation of a pre-functionalised cyclopropyl organoboron substrate.

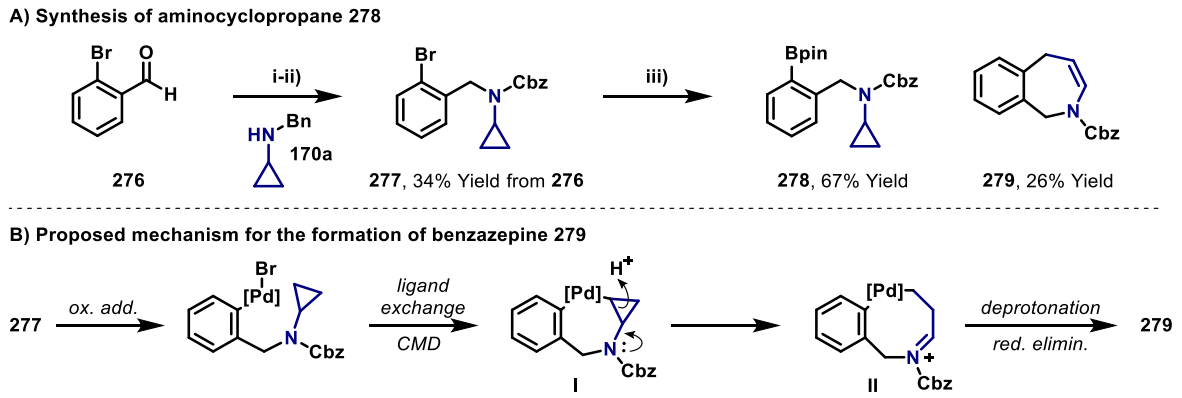
To explore the viability of the process proposed in Scheme 74B, cyclopropyl benzamide **275** bearing a pinacol boronic ester component was prepared using a 2-step sequence (Scheme 75). Conversion of boronic acid **274** to its corresponding pinacol boronic ester derivative (structure not shown), followed by HBTU-mediated amide coupling with amine **170a** afforded the target substrate **275** in 55% yield. Substrate **275** was then subjected to Rh(I)-catalysed carbonylative conditions; unfortunately, none of the desired benzofused heterocycle **273** formed after 72 h, and typically >70%

starting material **273** was recovered. Interestingly, the organoborane handle of **275** remained intact at 130 °C, and perhaps under more forcing conditions this challenging transformation might be achieved.



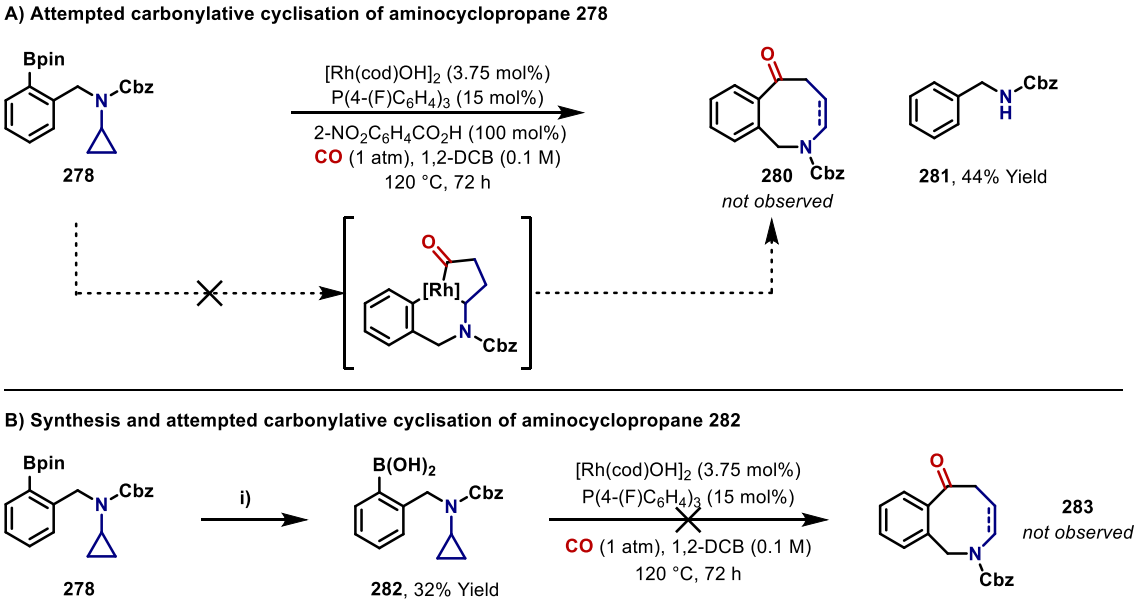
Scheme 75: Synthesis and attempted Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **275**. *Reagents and conditions*: i) pinacol, $MgSO_4$, THF, r.t., 20 h, 95%; ii) amine **170a**, HBTU, DIPEA, CH_2Cl_2, r.t., 16 h, 58%.

In concurrent studies, aminocyclopropane **278** bearing an *exo*-directing group was prepared and subjected to Rh(I)-catalysed carbonylative conditions (Scheme 76). Entry to aminocyclopropane **278** was enabled by reductive amination of 2-bromobenzaldehyde **276** with cyclopropylamine, followed by Cbz protection to afford **277** in 34% yield over the two steps. Next, Miyaura borylation of **277** under Pd(0)-catalysed conditions with B_2pin_2 furnished boronic ester **278** in 67% yield, alongside benzazepine **279** in 26% yield. Whilst the formation of benzazepine **279** is an interesting side-reaction, conceptually related studies have been disclosed in the literature.[192-194] A plausible mechanism for the formation of side-product **279** is presented in Scheme 76B. Following oxidative addition, ligand exchange and base-mediated concerted-metallation-deprotonation (CMD) of the cyclopropane C–H bond gives palladacycle **I**. Subsequent acid promoted ring opening of the cyclopropane gives 8-membered palladacycle **II**, from which deprotonation and C–C reductive elimination generates benzazepine **279**.[193-195]



Scheme 76: B) *Reagents and conditions*: i) amine **170a**, $NaHCO_3$, MeOH, reflux, 24 h *then* $NaBH_4$, 0 °C to r.t., 5 h, 45%; ii) Cbz-Cl, K_2CO_3, PhMe, 80 °C, 24 h, 76%; iii) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, B_2pin_2, K_2CO_3, 1,4-dioxane, 70 °C, 16 h.

Exposure of cyclopropylamide **278** to [Rh(cod)OH]$_2$/1,2-DCB conditions resulted in the sole formation of side-product **281** in 44% yield (Scheme 77A). The formation of **281** presumably occurs *via* protodeborylation and protodecyclopropanation of starting material **278**, but it is unclear as to the order of these side-reactions. To circumvent protodeborylation, the reaction was performed in the absence of 2-$NO_2C_6H_4CO_2H$, but this modification also failed to provide the desired heterocycle **280**. In order to promote the proposed transmetallation step, boronic ester **278** was converted to the less hindered boronic acid **282** (Scheme 77B). However, carbonylative cycloaddition of substrate **282** was not successful, and heterocycle **283** was not observed. Additionally, the inclusion of water as an additive to promote the transmetallation step was not successful.



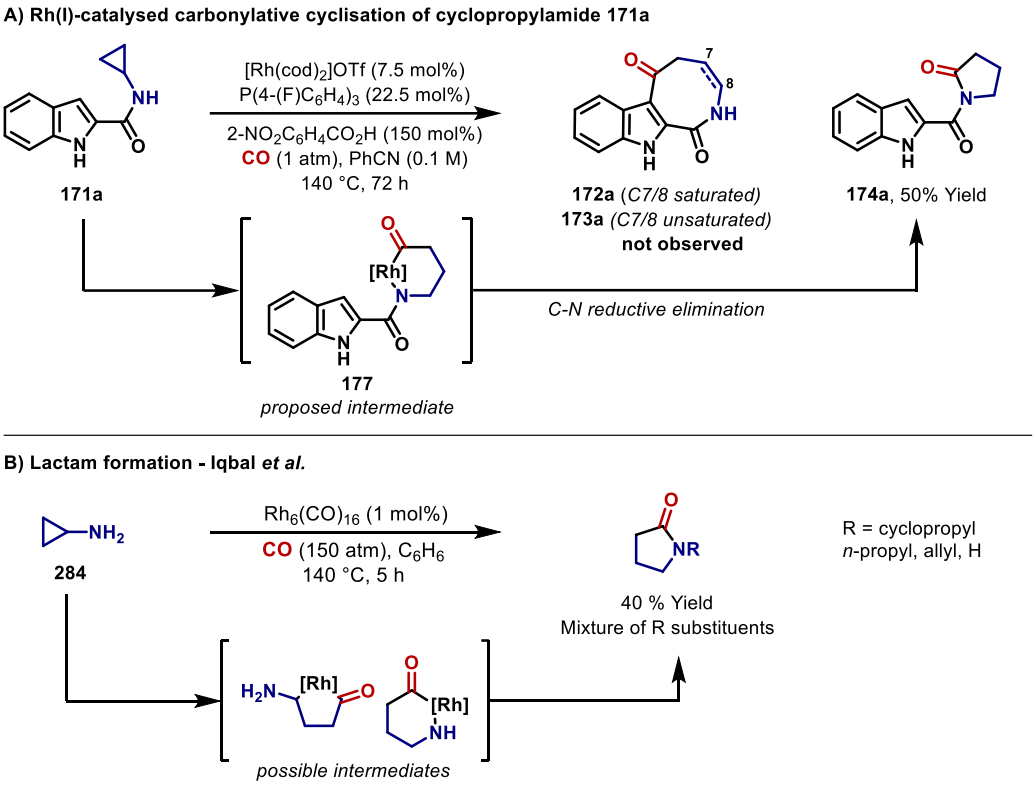
Scheme 77: B) *Reagents and conditions*: i) $NaIO_4$, THF:H_2O (5:1), r.t., 3 h.

So far, exploratory efforts to incorporate transmetallation into the "capture-collapse" heterocyclisations have been unsuccessful, and the reasons behind this remain unclear. Due to time constraints, boronic esters **275**/**278** and boronic acid **282** were evaluated under a limited number of conditions (total of 20 different sets of conditions across all substrates); therefore, additional investigations are required to ascertain the feasibility of this strategy. This research avenue will be investigated by the Bower group in due course.

3.3 Preliminary investigations into the synthesis of γ-lactams

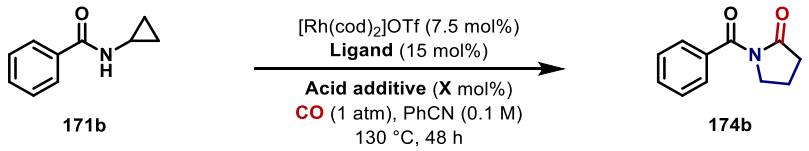
During the studies outlined in Chapter 2, it was discovered that secondary cyclopropylamide **171a** underwent Rh(I)-catalysed carbonylation to deliver γ-lactam **174a**, instead of 8-membered *N*-heterocycles **172a**/**173a** (Scheme 78). Whilst the mechanism for this transformation remains unclear, it was proposed that it might involve a putative 6-membered rhodacycle **177**, which following C–N reductive elimination affords the observed product **174a** (see Scheme 46 for proposed mechanism).

Although this result was unexpected, the formation of similar products under carbonylative conditions has previously been reported in the literature. Specifically, in 1971 Iqbal and co-workers reported that exposure of unsubstituted cyclopropylamine **284** to a neutral Rh(I)-catalyst and a high pressure of CO (150 bar) delivered a mixture of *N*-substituted γ-lactam products in 40% yield (Scheme 78B).[155] To date, no mechanistic work has been reported for this transformation; however, it is not unreasonable to assume it involves the intermediacy of a rhodacyclopentanone or an azarhodacyclohexanone.



Scheme 78: The formation of *N*-substituted γ-lactams by carbonylative ring expansion of aminocyclopropanes.

Compared to Iqbal's conditions, the formation of γ-lactam **174a** in 50% yield under an atmospheric pressure of CO is a significant improvement. Driven by this fact, a simplified phenyl derivative **171b** was selected as a test substrate for further optimisation studies and key preliminary findings are presented in Table 13.



171b 174b

Entry	Ligand	Acid additive	X (mol%)	Remaining 171b[a]	Yield 174b[a]
1[b]	$P(4\text{-}(F)C_6H_4)_3$	$2\text{-}NO_2C_6H_4CO_2H$	150	-	30%[c]
2	$P(4\text{-}(F)C_6H_4)_3$	$2\text{-}NO_2C_6H_4CO_2H$	30	-	26%
3	$P(4\text{-}(F)C_6H_4)_3$	$4\text{-}NMe_2C_6H_4CO_2H$	30	-	25%
4	$P(C_6F_5)_3$	$2\text{-}NO_2C_6H_4CO_2H$	30	-	20%
5	$P(C_6F_5)_3$	$4\text{-}NMe_2C_6H_4CO_2H$	30	-	21%
6	/	$4\text{-}NMe_2C_6H_4CO_2H$	30	-	26%
7	$P(4\text{-}(F)C_6H_4)_3$	/	/	observed by TLC	6%
8	/	/	/	10%	5%

Table 13: Preliminary optimisation results from the Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **171b**.[d] [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [b] The reaction temperature was 140 °C. [c] Isolated yield. [d] Phenyl derivative **171b** was synthesised by M. Shaw for an unrelated project.

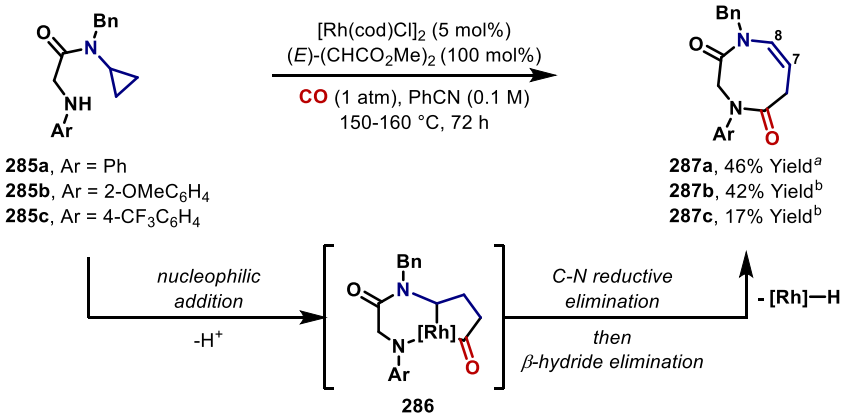
Subjection of phenyl substrate **171b** to $[Rh(cod)_2]OTf$, $P(4\text{-}FC_6H_4)_3$ and $2\text{-}NO_2C_6H_5CO_2H$ in PhCN under an atmosphere of CO delivered the desired γ-lactam adduct **174b** in 30% yield (Table 13, entry 1). It was found that decreasing the loading of $2\text{-}NO_2C_6H_5CO_2H$ afforded product **174b** in a slightly reduced yield of 26% (Table 13, entry 2). Changing the acid additive to $4\text{-}NMe_2C_6H_4CO_2H$ and/or the phosphine ligand to $P(C_6F_5)_3$ also failed to increase the yield of **174** (Table 13, entries 3–5). When the phosphine ligand was omitted, γ-lactam **174b** was obtained in a comparable yield of 26% (Table 13, entry 3 *vs.* 6). Conversely, when the reaction was performed in the absence of the acid additive or in the absence of both the acid additive and the phosphine ligand, the yield of γ-lactam **174b** decreased (Table 13, entries 7 and 8). Interestingly, these control experiments indicate that inclusion of a phosphine ligand is not essential for the formation of γ-lactam **174b**. However, due to poor mass balance and limited improvements in yield, no further work was undertaken on this transformation.

3.4 Conclusion and summary from the studies in Chapter 3

The research outlined in this chapter has described investigations towards the generality of the "capture-collapse" heterocyclisation strategy, in addition to preliminary studies towards a Rh(I)-catalysed formation of γ-lactams from cyclopropylamides. With regards to the former, efforts to extend the scope of the nucleophilic component beyond the N- and C-based nucleophiles that are described in initial reports,[20,21] have met with limited success. Indeed, cyclopropyl sulfamides 2**57a**–**d** and cyclopropyl pyridone **269** were completely ineffective in the "capture-collapse" heterocyclisation strategy (see Sections 3.2.1.1 and 3.2.1.3), thus making immediate extension of the protocol to other substrate types

challenging. On the other hand, exposure of cyclopropyl guanidine **263** to Rh(I)-catalysed carbonylative conditions led to a 7% *in situ* yield of 7-membered guanidine **264'** (Scheme 71). However, due to rhodacyclopentanone stability and deleterious side-reactions, this yield could not be improved upon. In related studies, preliminary investigations into a Rh(I)-catalysed carbonylative transmetallation-heterocyclisation strategy to access benzofused azocines were also unsuccessful. As stated in Section 3.2.2, the development of such a process is in its infancy, and further investigations are required in order to determine the feasibility of this strategy.

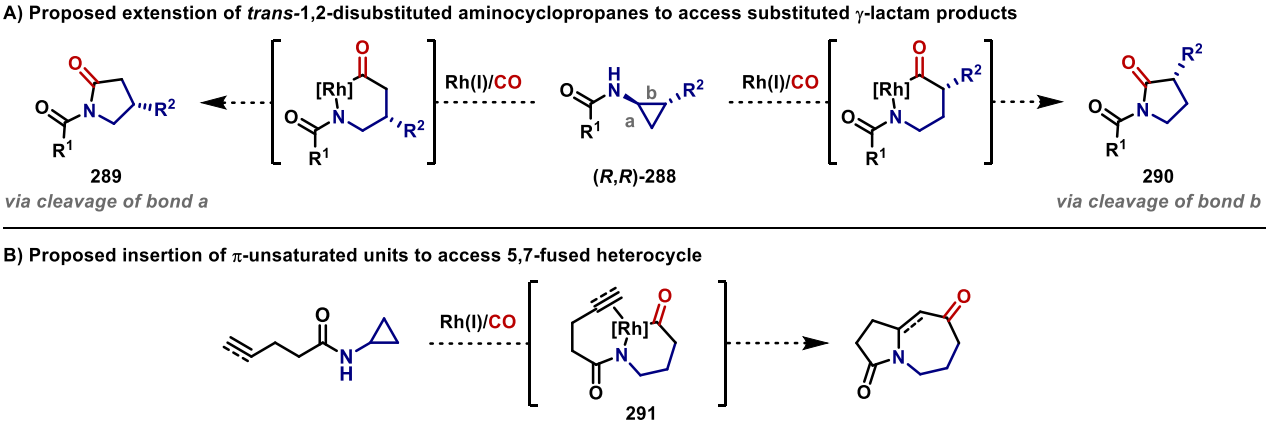
Following the work detailed in this chapter, subsequent research carried out in the Bower group has identified a related Rh(I)-catalysed "capture-collapse" heterocyclisation protocol. In particular, Dr. A. D. J. Calow and co-workers discovered that rhodacyclopentanone **286** generated from cyclopropylamides bearing a tethered aniline unit, underwent C–N reductive elimination to form C7/8 unsaturated 1,4-diazocanes **287a**–**c** in 17–46% yield (Scheme 79).[23] Of note, the corresponding C7/8 saturated products (structures not depicted) were not observed. The lowest efficiency obtained was for 4-CF_3 system **287c**, which indicates the importance of using a relatively nucleophilic aniline. Additionally, the processes are oxidative, and GCMS analysis revealed that turnover is achieved by reduction of (*E*)-$(CHCOOMe)_2$ to dimethyl succinate.



Scheme 79: 1,4-Diazocanes *via* C–N reductive elimination.

Finally, the initial experiments depicted in Scheme 78 and Table 13 provide proof-of principle for the formation of γ-lactam products by carbonylative ring expansion of secondary cyclopropylamides. Future studies should focus on improving the yield of lactam **174b** and also on gaining a better understanding of the reaction mechanism. Progress towards either of these goals should benefit the development and expansion of related processes. With this in mind, the ultimate goal for this process would be to evaluate enantiopure 1,2-disubstituted cyclopropylamide substrates (*e.g.* (***R,R***)-**288**) as a means to access γ-lactam products bearing stereodefined substituents (*e.g.* **289** *or* **290**) (Scheme 80). Additionally, these preliminary studies provide a compelling model upon which to design future reactions based on the intermediacy of a Rh(III)-hexacycle. In particular, it would stand to reason that

rhodacycle **291** might undergo carbometallation with tethered π-unsaturated units prior to reductive elimination, which, in turn, might provide 5,7-fused heterocycles (Scheme 80B). Not only would this broaden the scope of Rh(I)-catalysed cycloadditions, but also provide evidence of a catalytically generated 6-membered rhodacycle **177**/**291**. This research avenue will be investigated by the Bower group in due course.



Scheme 80: Proposed extension to access substituted γ-lactam derivatives and 5,7-fused heterocycles.

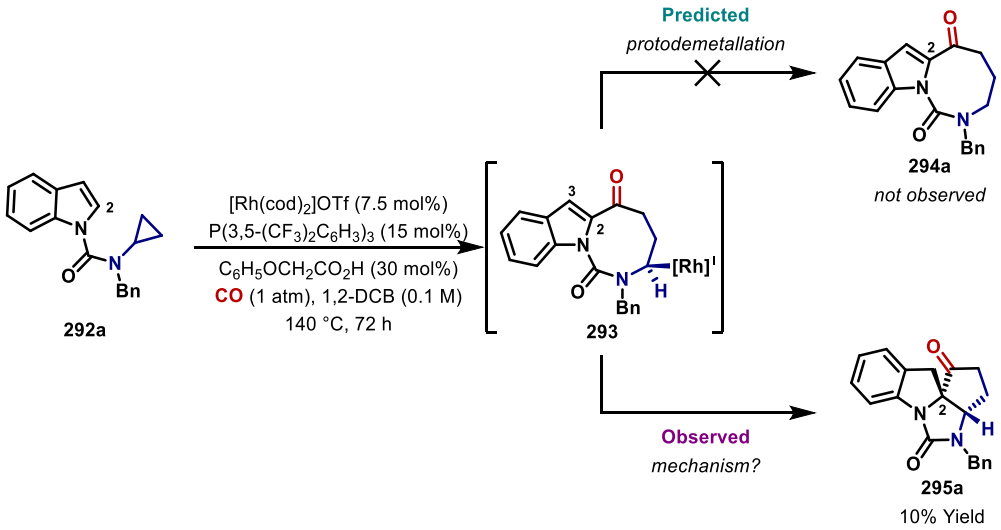
Chapter 4: Rhodacyclopentanones as linchpins for the synthesis of polyheterocycles

The work detailed in this chapter was conducted in collaboration with Dr. Gang-Wei Wang and Mr Tom Young. In order to give a complete overview of the work conducted, selected results obtained by G.-W. Wang and T. Young are provided. Results obtained by G.-W. Wang and T. Young are clearly indicated in the text and by footnotes under relevant Tables and Schemes. Aspects of this chapter have been adapted from a publication by G.-W. Wang et al.

*(J. Am. Chem. Soc. **2020**, 142, 1740-1745)*

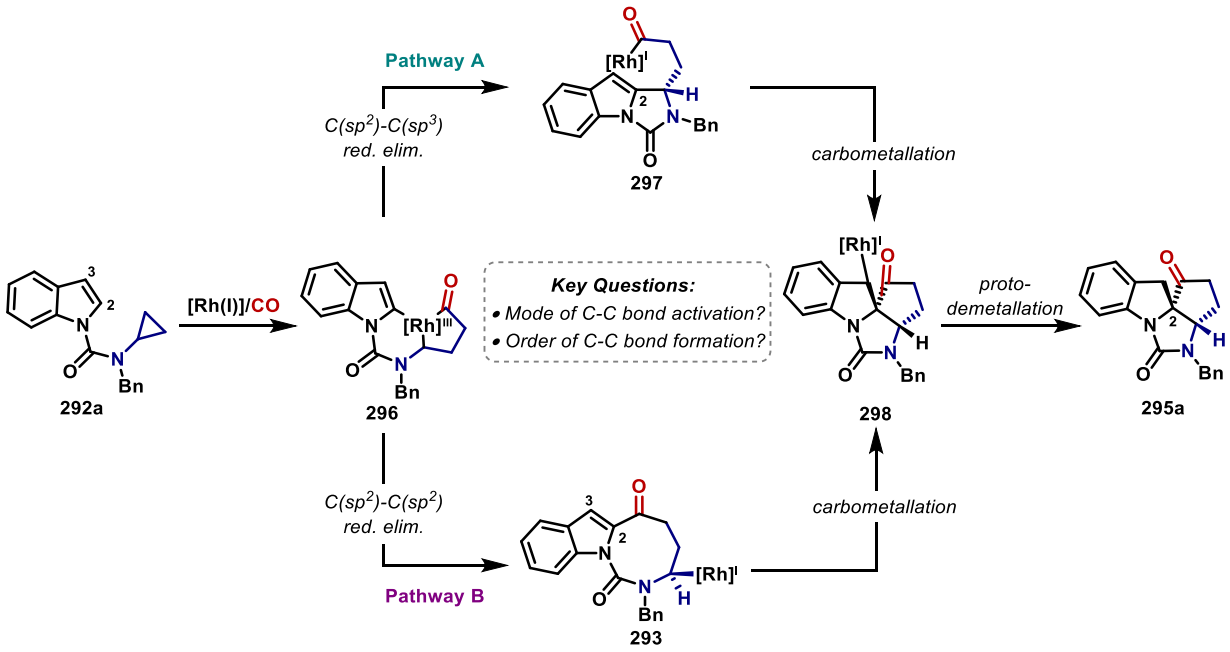
4.1 Discovery and proposed mechanism of a unique indole dearomatisation protocol

New strategies that enables the expeditious assembly of complex heterocycles are likely to be of significant interest to synthetic and medicinal chemists. In particular, methods that access underexplored regions of chemical space, such as sp^3-rich systems and polyheterocycles, are in high demand from the pharmaceutical sector as they present the opportunity to design novel compound libraries.[13,106,196] Within this context and as outlined previously (see Section 1.3.2 and Chapter 2), the Bower group has devised a strategy where cyclopropane-derived metallacycles engage tethered N- or C-based nucleophiles to generate 7- and 8-membered *N*-heterocycles (*e.g.* 1,3-diazepanes, benzazepanes, azocanes).[20,21] This strategy hinges on the tandem exploitation of strain relief and a metallabicycle templating effect to overcome the enthalpic and entropic barriers associated with medium-sized ring closures. In an effort to extend the applicability of these processes, G.-W. Wang examined the suitability of *N*-carbamoyl aminocyclopropane **292a** (Scheme 81). Under an atmosphere of CO, it was anticipated that aminocyclopropane **292a** would cyclise *via* putative Rh(I) intermediate **293** to furnish C2 annulated heterocycle **294a**, where C–H bond formation functions as the terminating step (**293** to **294a**). Somewhat surprisingly, it was found that aminocyclopropane **292a** was converted exclusively to complex polycycle **295a** in 10% yield when exposed to the combination of $[Rh(cod)_2]OTf$ (7.5 mol%), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (15 mol%) and $C_6H_5OCH_2CO_2H$ (30 mol%) under an atmosphere of CO in 1,2-DCB at 140 °C.



Scheme 81: The carbonylative dearomative cyclisation of indole **292a** delivered complex polycycle **295a**.[a] [a] Result obtained by G.-W. Wang.

The formation of polycycle **295a** posed an intriguing question regarding (i) the mode of C–C bond activation and (ii) the order of C–C bond formation. As shown in Scheme 82, two different mechanistic pathways were proposed for the formation of polycycle **295a**. In both proposals, it was postulated that initial formation of 6,5-rhodacycle **296** occurs *via* carbonyl directed carbonylative C–C bond activation of aminocyclopropane **292a** and C(sp^2)–H metallation; however, the exact order of these steps remained unknown. From intermediate **296**, it was reasoned that two distinct C–C bond forming sequences could access alkyl-Rh(I) intermediate **298**. In pathway A, 5-ring C(sp^2)–C(sp^3) reductive elimination to acyl-Rh(I) intermediate **297** is followed by 5-ring carbometallation of the indole C2–C3 π-system. Alternatively, in pathway B, 8-ring C(sp^2)–C(sp^2) reductive elimination to alkyl-Rh(I) intermediate **293** is followed by transannular carbometallation of the indole π-system. Finally, protodemetallation of alkyl-Rh(I) species **298** affords the observed product **295a**.



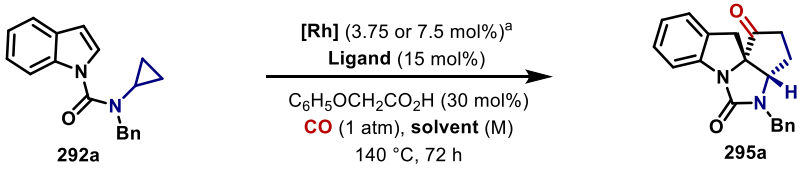
Scheme 82: Mechanistic rationale for the formation of polycycle **295a**.

In comparison with prior C–C bond activation triggered heterocyclisations,[20,21] this transformation is particularly noteworthy because it enables the concurrent formation of not one, but two new ring systems. Furthermore, this process is a unique example of the use of rhodacyclopentanones to effect indole dearomatisation chemistry and is notable for the formation of two new C–C bonds at the C-2 position.[197-199] Within this context, alternative catalytic methods capable of accessing similar molecular scaffolds generally require preinstallation of a substituent at the C-2 position.[200,201] Driven by the uniqueness of this transformation and the mechanistic implications, further investigations were warranted. To this end, optimisation and computational studies on the newly discovered reaction began in collaboration with G.-W. Wang and T. Young. It was anticipated that such analysis would not only provide key mechanistic insights, but also pave the way for expanding the reactivity modes of rhodacyclopentanones and thus unlock additional polyheterocyclic bond-forming processes.

4.2 Reaction optimisation and evaluation of scope

In collaboration with G.-W. Wang, systematic variation of reaction conditions was undertaken to improve the yield of polycycle **295a**. Over 150 conditions were evaluated and the most pertinent results are summarised in Tables 14 and 15. Initial investigations highlighted the importance of a non-coordinating solvent as no product was detected when 1,2-DCB was substituted for PhCN (Table 14, entries 1–2). Next, a representative range of phosphine ligands was assessed, and from this evaluation it was found that electron-rich and bidentate ligands were completely ineffective (Table 14, entries 3–5). Conversely, electron-deficient ligands performed better, with $P(C_6F_5)_3$ emerging as the most efficient ligand, affording polycycle **295a** in 46% yield (Table 14, entry 7). Reducing the reaction

temperature to 130 °C further increased the yield of **295a** to 53% (Table 14, entry 8). These results indicate that an electron-deficient Rh-complex is required; consequently, it was anticipated that further reaction efficiency might be achieved by employing a Rh(I)-catalyst with a more dissociating counterion.[202] However, switching to a BARF counterion was detrimental to the yield of polycycle **295a** (Table 14, entries 7 *vs.* 9). Alternative Rh(I)-sources, including $[Rh(cod)_2]BF_4$, $[Rh(cod)Cl]_2$ and $[Rh(cod)OH]_2$, were also ineffective (Table 14, entries 10–12).

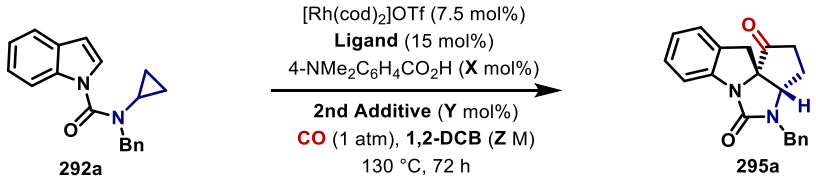


Entry	[Rh]	Ligand	Solvent (M)	Remaining 292a[b]	Yield 295a[b]
1	$[Rh(cod)_2]OTf$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	1,2-DCB (0.2 M)	80%	10%[d]
2	$[Rh(cod)_2]OTf$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	PhCN (0.2 M)	>95%	-
3	$[Rh(cod)_2]OTf$	$P(4\text{-}(OMe)C_6H_4)_3$	1,2-DCB (0.2 M)	>95%	-
4	$[Rh(cod)_2]OTf$	$P(C_6H_5)_3$	1,2-DCB (0.2 M)	>95%	<5%
5	$[Rh(cod)_2]OTf$	*rac*-BINAP[c]	1,2-DCB (0.2 M)	>95%	-
6	$[Rh(cod)_2]OTf$	$P(4\text{-}(F)C_6H_4)_3$	1,2-DCB (0.2 M)	77%	11%
7	$[Rh(cod)_2]OTf$	$P(C_6F_5)_3$	1,2-DCB (0.2 M)	-	46%[d]
8[e]	$[Rh(cod)_2]OTf$	$P(C_6F_5)_3$	1,2-DCB (0.2 M)	9%	53%
9	$[Rh(cod)_2]BARF$	$P(C_6F_5)_3$	1,2-DCB (0.2 M)	35%	14%
10	$[Rh(cod)_2]BF_4$	$P(C_6F_5)_3$	1,2-DCB (0.2 M)	>95%	<5%
11	$[Rh(cod)Cl]_2$	$P(C_6F_5)_3$	1,2-DCB (0.2 M)	>95%	<5%
12	$[Rh(cod)OH]_2$	$P(C_6F_5)_3$	1,2-DCB (0.2 M)	>95%	<5%

Table 14: Selected optimisation results for the Rh(I)-catalysed carbonylative polycyclisation of indole **292a**.[f] [a] 3.75 mol% was used for dimeric Rh(I)-catalysts and 7.5 mol% was used for monomeric Rh(I)-catalysts. [b] The yield was determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [c] 7.5 mol% of *rac*-BINAP was used. [d] Isolated yield. [e] The reaction temperature was 130 °C. [f] Results obtained by G.-W. Wang.

Subsequently, a broad screen of acid additives encompassing carboxylic (*e.g.* benzoic acids, hexanoic acid, $AdCO_2H$, fumaric acid), sulfonic (*e.g.* TsOH) and phosphoric (*e.g.* $(C_6H_5O)_2P(O)OH$) acids was conducted. Although no consistent trends were identified with respect to the steric environment, acidity or coordinating ability of the acid additives, $4\text{-}NMe_2C_6H_4CO_2H$ emerged as the preferred candidate, delivering product **295a** in 55% yield (Table 15, entry 1). Possible roles of the acid additive are discussed in Section 4.3. A series of control experiments verified the necessity of the acid additive but not the phosphine ligand. Specifically, in the absence of $4\text{-}NMe_2C_6H_4CO_2H$, no product was formed (Table 15, entry 2); whereas, in the absence of the phosphine ligand, polycycle **295a** was

formed in an enhanced yield of 71% (Table 15, entry 3). Further optimisation studies evaluated the loading of 4-$NMe_2C_6H_4CO_2H$ and the reaction concentration. Whilst increasing the amount of 4-$NMe_2C_6H_4CO_2H$ from 15 mol% to 30 mol% had a minor effect on the yield of **295a** (71% *vs.* 68%, Table 15, entries 3–4), additional increments led to diminished yields (Table 15, entries 5–6). Decreasing the concentration to 0.1 M with 30 mol% 4-$NMe_2C_6H_4CO_2H$ led to a small improvement in the yield of **295a** (73% yield, Table 15, entry 7). However, an increase in concentration to 0.3 M was detrimental to the yield of **295a** (Table 15, entry 8). Finally, it was considered that the reaction might be sensitive to adventitious water as Rh(I)-catalysts are known to form hydroxy-bridged dimers in the presence of water;[203] therefore, drying agents were employed in an attempt to exclude water from the system (Table 15, entries 9–10). To this end, the inclusion of 100 mol% of Na_2SO_4 provided a beneficial and reproducible effect, affording the target polyheterocycle **295a** in 81% yield Table 15, entry 9. Thus, optimal carbonylative conditions involved treatment of **295a** with $[Rh(cod)_2]OTf$ (7.5 mol%), 4-$NMe_2C_6H_4CO_2H$ (30 mol%), Na_2SO_4 (100 mol%) in 1,2-DCB (0.1 M) at 130 °C.



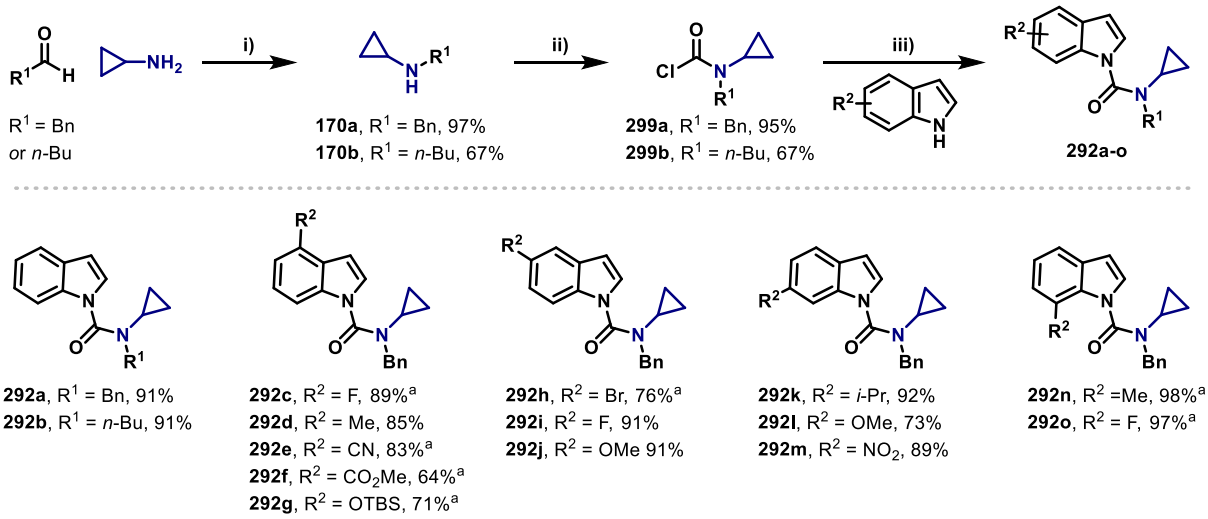
Entry	Ligand	X (mol%)	2nd Additive (Y mol%)	1,2-DCB (Z M)	Remaining 292a[a]	Yield 295a[a]
1	$P(C_6F_5)_3$	15	/	0.2 M	5%	55%
2	$P(C_6F_5)_3$	/	/	0.2 M	>95%	-
3	/	15	/	0.2 M	-	71%
4	/	30	/	0.2 M	6%	68%[b]
5	/	60	/	0.2 M	18%	60%
6	/	100	/	0.2 M	33%	41%
7	/	30	/	0.1 M	-	73%[b]
8	/	30	/	0.3 M	-	48%
9	/	30	Na_2SO_4 (100 mol%)	0.1 M	-	81%[b]
10	/	30	$MgSO_4$ (100 mol%)	0.1 M	-	62%

Table 15: Selected optimisation results for the Rh(I)-catalysed carbonylative polycyclisation of indole **292a**.[c] [a] The yield was determined by ^1H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. [b] Isolated yield. [c] Results obtained by G.-W. Wang.

4.2.1 Synthesis and evaluation of indole *N*-carbamoyl aminocyclopropanes

Having established a viable protocol, attention turned to evaluating the scope and functional group tolerance of substituents on the indole unit. To facilitate these studies, G.-W. Wang developed a three-step sequence to synthesise a variety of *N*-carbamoyl substrates **292b**–**o** (Scheme 83). The sequence

began with reductive amination of cyclopropylamine with benzaldehyde or butyraldehyde to afford secondary amines **170a**–**b** in excellent yield. From here, treatment of amines **170a**–**b** with triphosgene, followed by 1,2-addition of the required indole derivative, delivered *N*-carbamoyl substrates **292b**–**o** in 64–98% yield.



Scheme 83: *Reagents and conditions*: i) corresponding aldehyde, $NaHCO_3$, MeOH, reflux, 18 h *then* $NaBH_4$, 0 °C to r.t., 18 h; ii) triphosgene, pyridine, toluene, 0 °C, 10 mins *then* **170a** *or* **170b**, 0 °C to r.t., 2 h; iii) corresponding indole, NaH, THF, 0 °C to r.t., 1 h *then* **299a** *or* **299b**. [a] Synthesised by G.-W. Wang.

With a diverse array of indole derivatives **292a–o** in hand, they were assessed in the Rh(I)-catalysed carbonylative polycyclisation protocol. In general, both electron-donating and electron-withdrawing substituents were accommodated on the indole ring, producing polycyclic targets **295a**–**k** in good to excellent yield (45–83%) and as single diastereomers (Table 16). The structure of **295k** was confirmed unambiguously by single crystal X-ray diffraction. Notably, potentially labile groups remained intact; for example, cyclisation of ester **292f**, protected alcohol **292g** and aryl bromide **292h** proceeded efficiently to afford polycycles **295f**–**h** in 45–57% yield. The inclusion of electron-withdrawing substituents at the C6 position of the indole unit led to reduced efficiencies, such that C6-nitro analogue **295m** was formed in only 18% yield. This decrease in efficiency is likely due to specific electronic requirements of the indole core. Likewise, C7-substituted derivatives **292n** and **292o** also participated with lower efficiency, providing adducts **295n** and **295o** in 18% and 21% yield respectively.

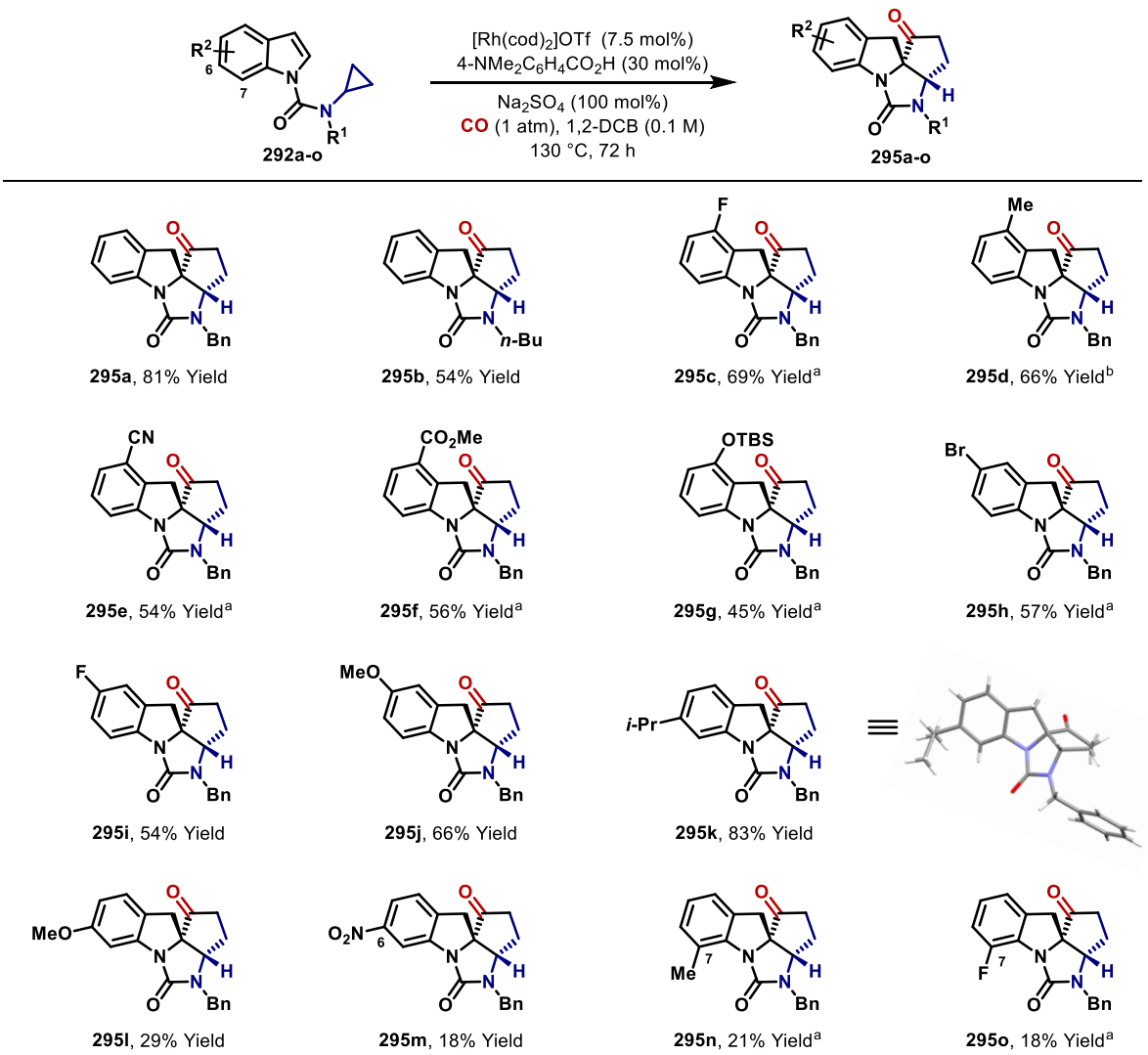


Table 16: Scope of the indole component in the carbonylative dearomative polycyclisation. [a] Synthesised by G.-W. Wang. [b] The reaction temperature was 140 °C.

4.2.2 Evaluation of *trans*-1,2-disubsituted aminocyclopropanes and trisubstituted aminocyclopropanes

Encouraged by these results, further substrate scope involving *trans*-1,2-disubstituted and trisubstituted aminocyclopropanes was investigated by G.-W. Wang (Table 17). A range of *trans*-1,2-disubstituted systems ***trans*-292p**–**r** underwent polycyclisation *via* selective C–C bond activation of the less hindered bond (*bond* ***a*** of ***trans*-292p**–**r**) to deliver products **295p**–**r** in 52–68% yield and with excellent diastereocontrol (Table 17A). Of particular note is the enantiospecific conversion of enantioenriched ***trans*-292q** to polycycle **295q** (98.5:1.5 e.r.). The same catalyst system was extended to include trisubstituted cyclopropanes ***trans*-292s** and ***trans*-292t**, with the ensuing carbonylative polycyclisations effecting efficient desymmetrisation to afford polycyclic targets **295s** and **295t** in 55% and 40% yields and with complete diastereocontrol (Table 17B). Even more impressively, in the case of non-symmetrical trisubstituted cyclopropane ***trans*-292u**, the protocol was highly selective for

activation of the benzylic C–C bond (*bond **a*** of ***trans*-292u**), which led to the regioselective formation of intricate polycycle **295u** in 52% yield and with excellent levels of diastereocontrol (Table 17C). The structure of **295u** was unambiguously determined by X-ray crystallography.

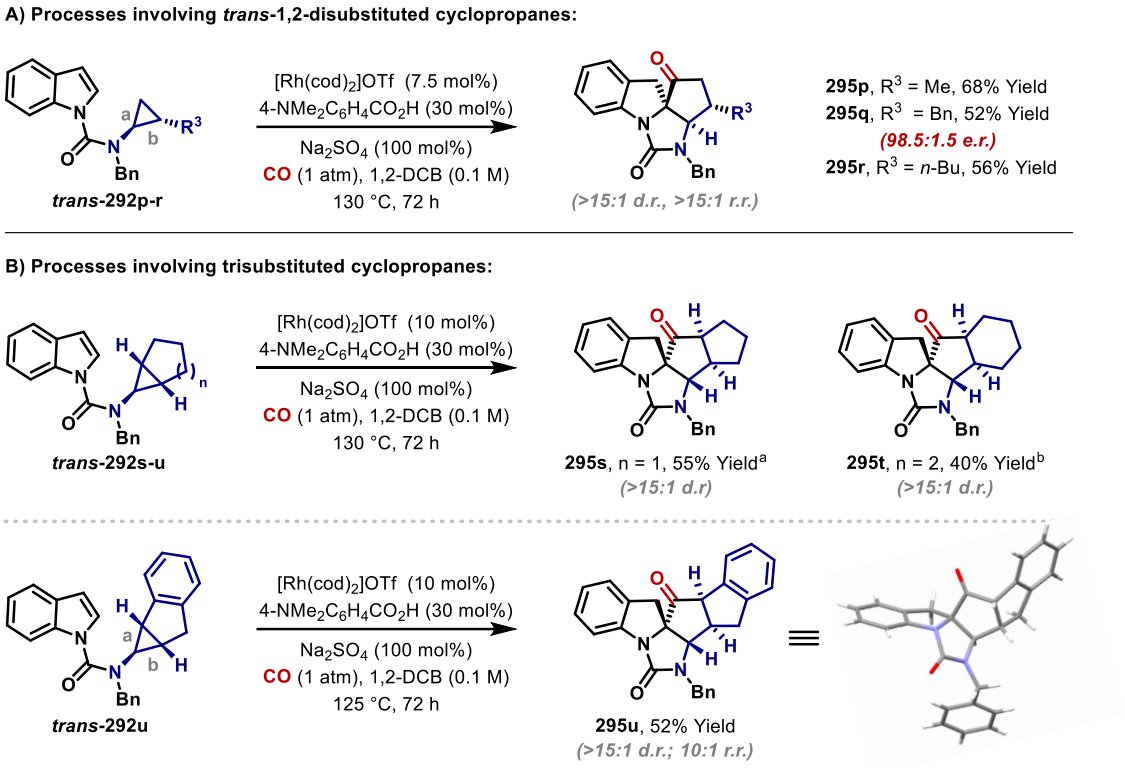


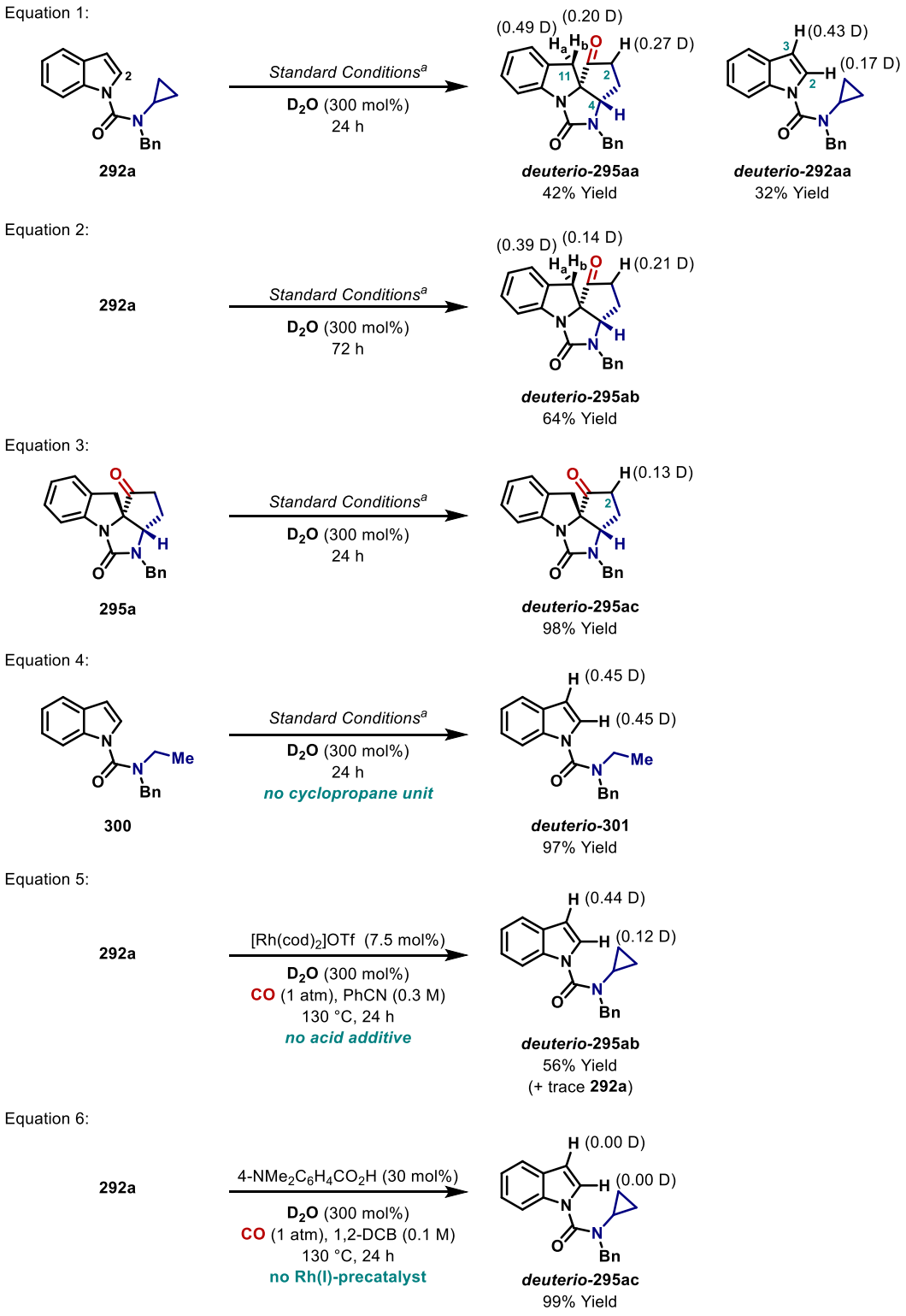
Table 17: Evaluation of *trans*-1,2-disubstituted cyclopropanes and trisubstituted cyclopropanes.[c] [a] The reaction was run in 1,2-DCB (0.2 M). [b] The reaction temperature was 150 °C. [c] Results obtained by G.-W. Wang.

4.3 Mechanistic studies

Having appraised the scope of this unique carbonylative polyheterocyclisation, attention turned to investigate its mechanism. To this end, both deuterium exchange experiments and density functional theory (DFT) calculations were performed to aid elucidation of key mechanistic steps.

4.3.1 Deuterium exchange experiments

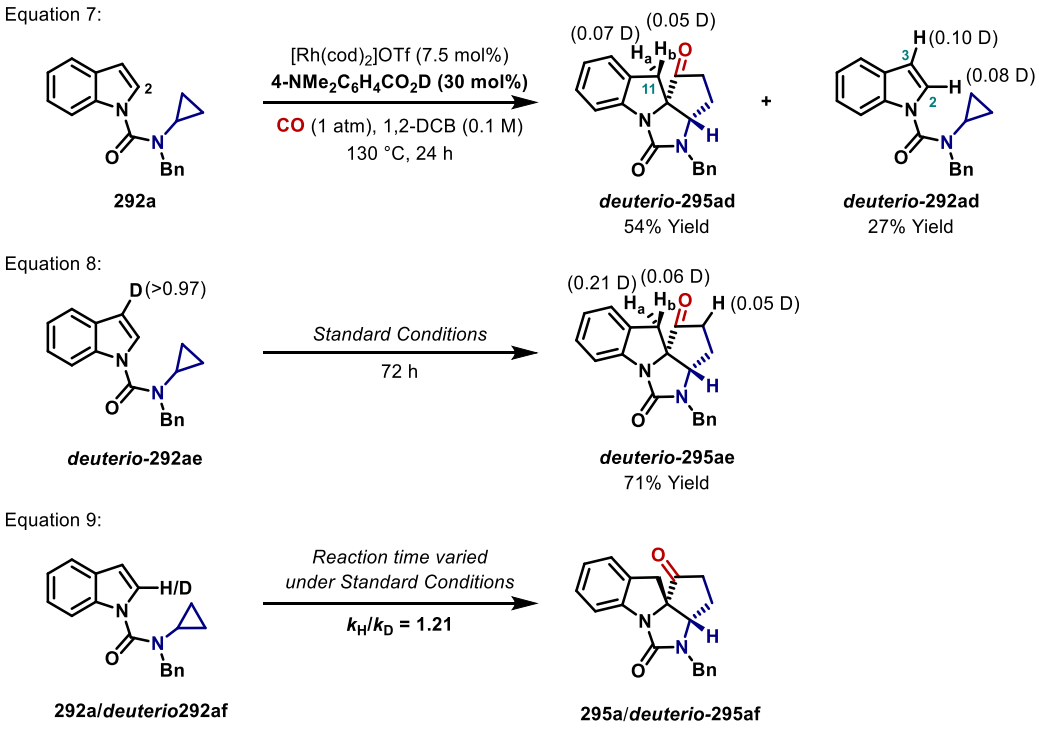
Initially, using indole **292a** as a model substrate, a series of deuterium exchange experiments were performed in collaboration with G.-W. Wang (Schemes 84 and 85). After 24 hours, carbonylative polycyclisation of **292a** in the presence of D_2O (300 mol%) delivered ***deuterio*-295aa** and ***deuterio*-292aa** in 42% and 32% yield (Equation 1). For ***deuterio*-292aa**, deuterium incorporation was observed at C2–H (17%) and C3–H (43%). Control experiments verified that deuterium incorporation at C2–H and C3–H of ***deuterio*-295aa** is dependent on the presence of the Rh(I)-catalyst, and not the benzoic acid additive or the cyclopropane unit (Equations 4–6). These results support an exchange pathway involving reversible C2–H activation of **292a**. For ***deuterio*-295a**, deuterium incorporation was observed at C2–H (27%), C11–H_a (49%) and C11–H_b (20%). When the reaction was run at full conversion in the presence of D_2O (300 mol%), similar levels of deuterium incorporation were observed for ***deuterio*-295ab** (compare Equation 1 *vs.* Equation 2). To confirm that exchange at the C2–H position of ***deuterio*-295aa/295ab** is due to enolisation of the product, pure cyclised product **295a** was re-subjected to the standard reaction conditions in the presence of D_2O (300 mol%). Analysis of recovered ***deuterio*-295ac** revealed 13% deuterium incorporation at C2–H, in support of this hypothesis (Equation 3). The question remained as to how to account for the deuterium incorporation at C11–H_a and C11–H_b of ***deuterio*-295a/295ab**. It was proposed that incorporation at the former position most likely occurs at the stage of **292a** as comparable levels of deuterium incorporation are detected at C3–H of ***deuterio*-292aa** (49% D for ***deuterio*-295aa** and 39% for ***deuterio*-295ab** *vs.* 43% D for ***deuterio*-292aa**). On the other hand, it was reasoned that incorporation at the latter position is consistent with *syn*-stereospecific carbometallation of the C2–C3 π-system prior to protodemetallation (*i.e.* **293** to **298**, see Scheme 82). Moreover, nOe analysis of ***deuterio*-295aa** showed a strong correlation between C4–H and C11–H_b, thus confirming the relative stereochemistry of C11–H_a/C11–H_b and C4–H.



Scheme 84: Mechanistic experiments.[b] *Standard conditions*: $[Rh(cod)_2]OTf$ (7.5 mol%), 4-$NMe_2C_6H_4CO_2H$ (30 mol%), Na_2SO_4 (100 mol%), CO (1 atm), 1,2-DCB (0.1 M), 130°C. [a] The reaction was run without Na_2SO_4. [b] The results from equations 1–6 were obtained by G.-W. Wang.

Guided by previous reports,[20,21] it was proposed that the proton required for the protodemetallation step originates from either the acid additive or C2–H of **292a**. Indeed, when the

carbonylative polyheterocyclisation of **292a** was performed using 30 mol% 4-$NMe_2C_6H_4CO_2D$ (prepared by dissolving 4-$NMe_2C_6H_4CO_2H$ in d_4-methanol and concentrating *in vacuo* three times), low but detectable levels of deuterium incorporation were observed at C11–H_a and C11–H_b of ***deuterio*-295ad** (Equation 7). Additional roles of the acid additive, such as acting as a carboxylate ligand to facilitate CMD-type cleavage of the C2–H bond cannot be discounted.[204] Additionally, when ***deuterio*-292ae** was exposed to the standard reaction conditions, the deuterium label was predominantly transferred to C11–H_a and not C11–H_b (Equation 8). Finally, a small kinetic isotope effect (k_H/k_D = 1.21) was observed by independently exposing equimolar amounts of **292a** or ***deuterio*-292af** to the standard conditions and stopping the reaction at specific time points (Equation 9), thus indicating that cleavage of the C–H bond is not turnover-limiting.[160]



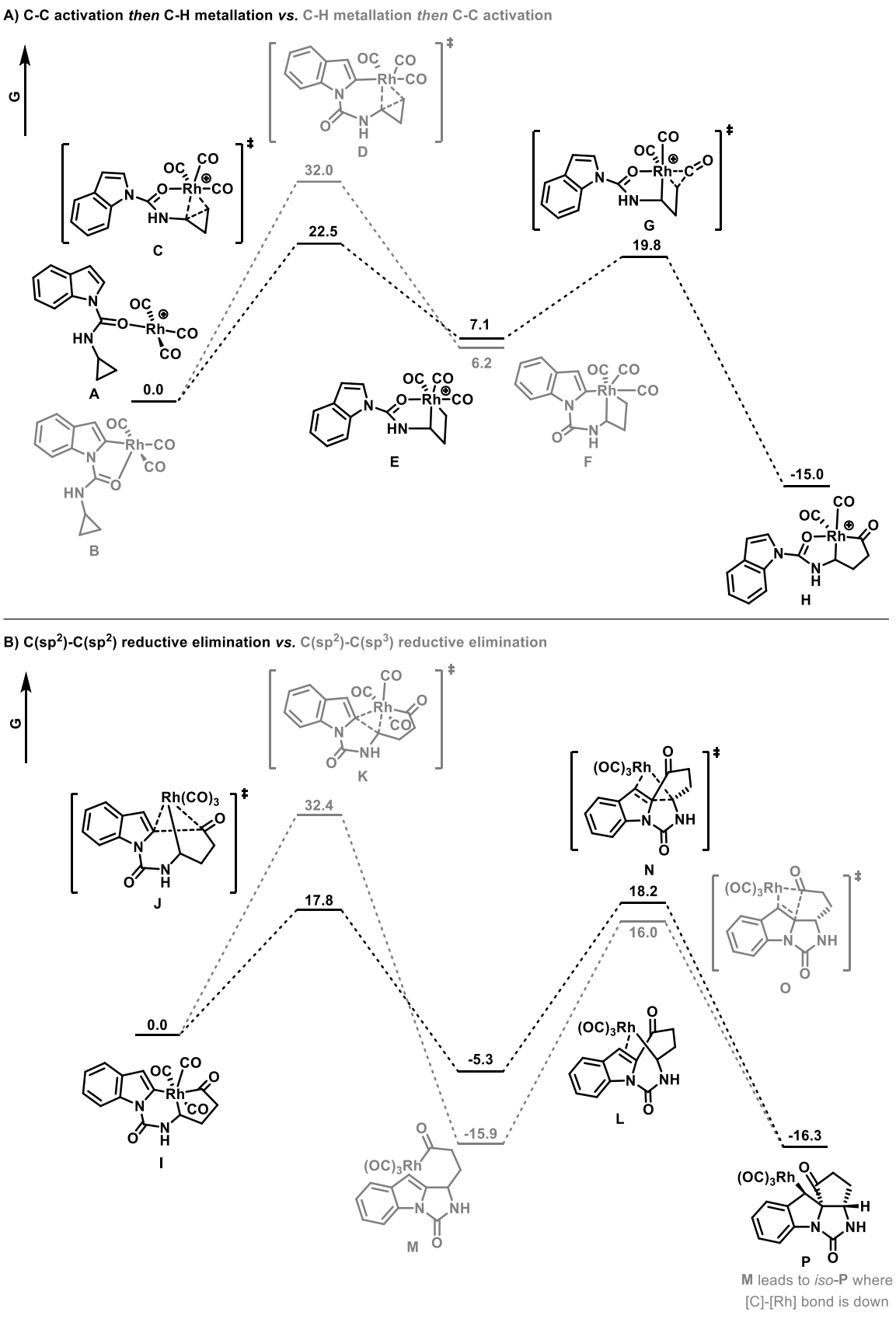
Scheme 85: Mechanistic experiments.[a] *Standard conditions*: [Rh(cod)$_2$]OTf (7.5 mol%), 4-$NMe_2C_6H_4CO_2H$ (30 mol%), Na_2SO_4 (100 mol%), CO (1 atm), 1,2-DCB (0.1 M), 130 °C. [a] The results from Equations 8 and 9 were obtained by G.-W. Wang.

4.3.2 DFT computational studies

The experiments depicted in Schemes 84 and 85 are consistent with a mechanistic pathway involving stereoretentive protodemetallation of a C11-alkyl-Rh(I) species (*i.e.* species **298**); however, convincing evidence for the steps leading up to this intermediate could not be obtained. As such, questions remained regarding (i) the mode of C–C bond activation and (ii) the C–C bond forming sequence from the putative rhodacycle **296**. To address these issues, DFT calculations were conducted by T. Young (Scheme 86). For these studies, several points should be noted. Firstly, as the exact ligand environment around the

rhodium centre cannot be confirmed, these calculations are intended to be comparative and not absolute. Secondly, as it difficult to compare the relative stabilities of intermediates with different overall charge (neutral *vs.* cationic), due to large differences in solvation energies,[205,206] it is assumed that on the basis of experimental evidence, C–H metallation is reversible. Consequently, it is presumed that species **A** and **B** are not separated by more than a few kcal mol^{-1} and hence, zero points in energy can be applied to these species.

Initially, we wanted to understand if a reaction pathway involving C–C bond activation followed by C–H metallation is favoured *or* if C–H metallation followed by C–C bond activation is preferred (Scheme 86A). It was calculated that carbonyl directed C–C bond activation of **A** to form **E** is endergonic (ΔG = 7.1 kcal mol^{-1}), with a barrier of 22.5 kcal mol^{-1}. From complex **E**, migratory insertion of CO proceeds through transition state **G** with a lower energy barrier (12.7 kcal mol^{-1} *vs.* 15.4 kcal mol^{-1} for **E** to **A**) to give rhodacyclopentanone **H** (ΔG = -22.1 kcal mol^{-1}). In accordance with the deuterium labelling studies outlined in Equations 4 and 5, it was considered that the C2–H metallation complex akin to **B** is accessible; but, in this scenario, subsequent C–C bond activation *via* transition state **D** is prohibitively high (ΔG = 32 kcal mol^{-1}). Therefore, this pathway was deemed unlikely. Consequently, the alternate pathway involving carbonyl directed C–C bond activation to generate rhodacyclopentanone **H** is favoured, from which straightforward C–H metallation gives complex **I** (*cf.* intermediate **296**, see Scheme 82). At this stage, two different bond forming sequences were envisaged to access the critical alkyl-Rh(I) species **P**/***iso*-P** (Scheme 86B). In one case, 5-ring C(sp^2)–C(sp^3) reductive elimination to acyl-Rh(I) species **M** is followed by 5-ring carbometallation of the indole C2–C3 π-system *via* transition state **O**. It was calculated that the energy required for this transformation is high (32.4 kcal mol^{-1} and 31.9 kcal mol^{-1} respectively); therefore this pathway is unlikely to be operational. On the other hand, complex **P** can be accessed by C(sp^2)–C(sp^2) reductive elimination to complex **L**, followed by transannular carbometallation of the indole C2–C3 π -system *via* transition state **N**. Interestingly, despite the formation of a strained 8-membered ring in complex **L**,[207] both of these steps are energetically accessible with barriers of 17.8 kcal mol^{-1} and 24.5 kcal mol^{-1}. As a result of these studies, it was deduced that C–C bond formation *via* C(sp^2)–C(sp^2) reductive elimination from **I** is favoured. The nature of the C–C reductive elimination step is in line with previous studies concerning the formation of 8-membered *N*-heterocycles (see Chapter 2), as well as other studies regarding the relative ease of C(sp^2)–C(sp^2) *vs.* C(sp^2)–C(sp^3) reductive elimination from Rh(III)-intermediates.[208] Counter to perceived expectations, it is remarkable that transannular carbometallation of complex **L** to **P** overrides terminating protodemetallation from complex **L** (*i.e.* formation of **294a** is prohibited, see Scheme 81).[207] Additionally, the feasibility of the C(sp^2)–C(sp^3) reductive elimination pathway was further ruled out because experimentally no products originating from decarbonylation of intermediates akin to **M** were detected.[209]

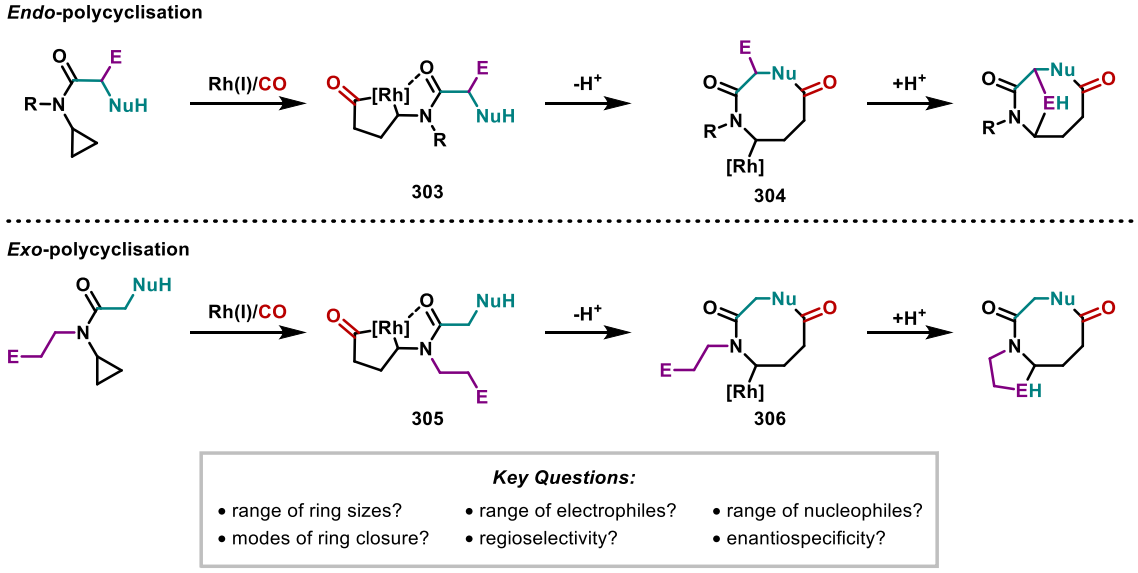


Scheme 86: DFT analysis of C–C bond activation and C–C bond forming pathways.[a] Calculations performed at the B3PW91-D3BJ/6-311+G(2d,p),Rh(LANTZ(f))/SMD(DCB)//B3PW91-D3BJ/6¬31G(d),Rh(MWB28) level

of theory, with thermochemical corrections calculated at T = 403 K and a 1 M standard state. [a] Computational analysis was conducted by T. Young.

4.4 The design and development of Rh(I)-catalysed carbonylative *exo*-polycyclisation cascades

The studies outlined so far in this chapter have demonstrated that rhodacyclopentanone intermediates function as linchpins for the dual construction of two new ring systems of polyheterocycles. In particular, the carbonylative cyclisation of aminocyclopropane **292a** to polycycle **295a** was justified by invoking *endo*-polycyclisation of key alkyl-Rh(I)-intermediate **293** (*cf.* **L**/**N**, see Scheme 86B) onto the C2–C3 π-system of the indole unit. Building upon this discovery, it was imagined that further classes of polycyclisation cascade might be achieved by varying the position and nature of the nucleophilic or electrophilic component of suitable aminocyclopropane substrates. By exploring this strategy, a suite of innovative *endo*- or *exo*-polycyclisation cascades was envisaged (Scheme 87) where the electrophilicity of rhodacyclopentanones **303** or **305** facilitates the first annulation, and their latent nucleophilicity enables the second (*via* **304**/**306**). Accordingly, attention shifted to investigate how we might steer the reaction to undergo selective *endo- or exo*-trapping of catalytically generated alkyl-Rh(I) species.

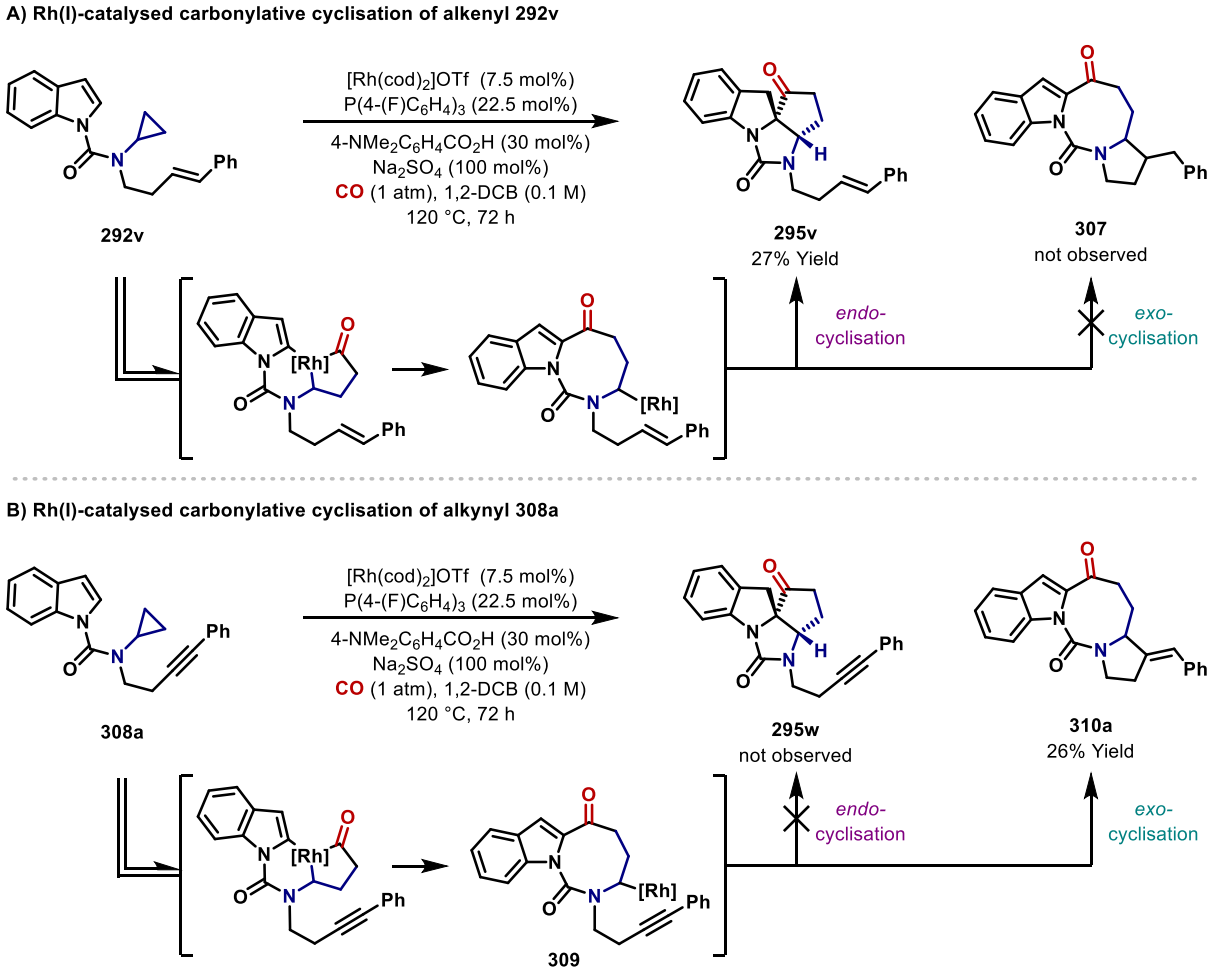


Scheme 87: Proposed extension to related Rh(I)-catalysed polycyclisation processes. NuH = nucleophile. E = electrophile.

4.4.1 Development of a prototype Rh(I)-catalysed carbonylative *exo*-polycyclisation cascade

To gauge the feasibility of this strategy, G.-W. Wang prepared alkenyl **292v** and alkynyl **308a** systems and exposed them to the optimised carbonylative conditions (Scheme 88). In these exploratory reactions, the judicious inclusion of P(4-FC_6H_4)$_3$ (15 mol%) was necessary to suppress *endo*-cyclisation *via* the

indole π-system of **292v**/**308a**. Under these conditions, alkenyl **292v** cyclised to form dearomatised polycycle **295v** as the sole product in 27% yield, and the product arising from carbometallation of the alkene tether (*i.e.* 8,5-fused polycycle **307**) was not observed. In comparison, alkynyl **308a** cyclised exclusively *via exo*-selective carbometallation of the alkyne unit to afford 8,5-fused polyheterocycle **310a** in 26% yield. To account for the difference in reactivity, it was reasoned that the strongly π-coordinating alkyne unit of **308a** promotes selective *exo*-carbometallation over *endo*-carbometallation of the indole π-system. Moreover, polyheterocycle **310a** was formed as a single geometric isomer, further validating the proposed *syn*-stereospecific carbometallation step from intermediate **309** (*cf.* intermediate **293**, Scheme 82). When the same transformations were performed in the absence of the ligand P(4-FC_6H_4)$_3$ (*i.e.* under the optimised conditions outlined in Table 15), the yield of polycycle **295v** increased to 42% yield, whereas **310a** was not observed.



Scheme 88: Development of a prototype Rh(I)-catalysed carbonylative C–C bond activation triggered *exo*-polycyclisation.[a] [a] Results obtained by G.-W. Wang.

Having demonstrated proof-of-principal for a Rh(I)-catalysed carbonylative *exo*-polycyclisation cascade, subsequent studies focused on improving the yield of polyheterocycle **310a**. Further optimisation studies, carried out by G.-W. Wang, determined that the yield of 8,5-fused

polycycle **310a** could be increased to 55% by replacing P(4-FC_6H_4)$_3$ with P(3,5-$(CH_3)_3C_6H_3$)$_3$ (Table 18). Under these optimised conditions, the reaction sequence was extended to related polycyclisation processes, delivering indole- and pyrrole-based systems **310b**–**e** in 39–82% yield (Table 18).

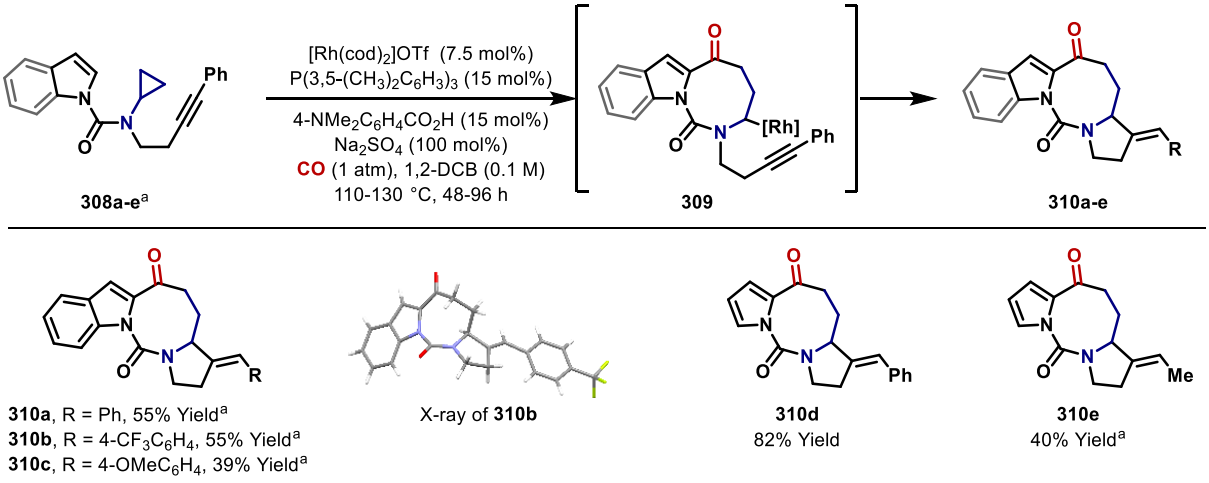
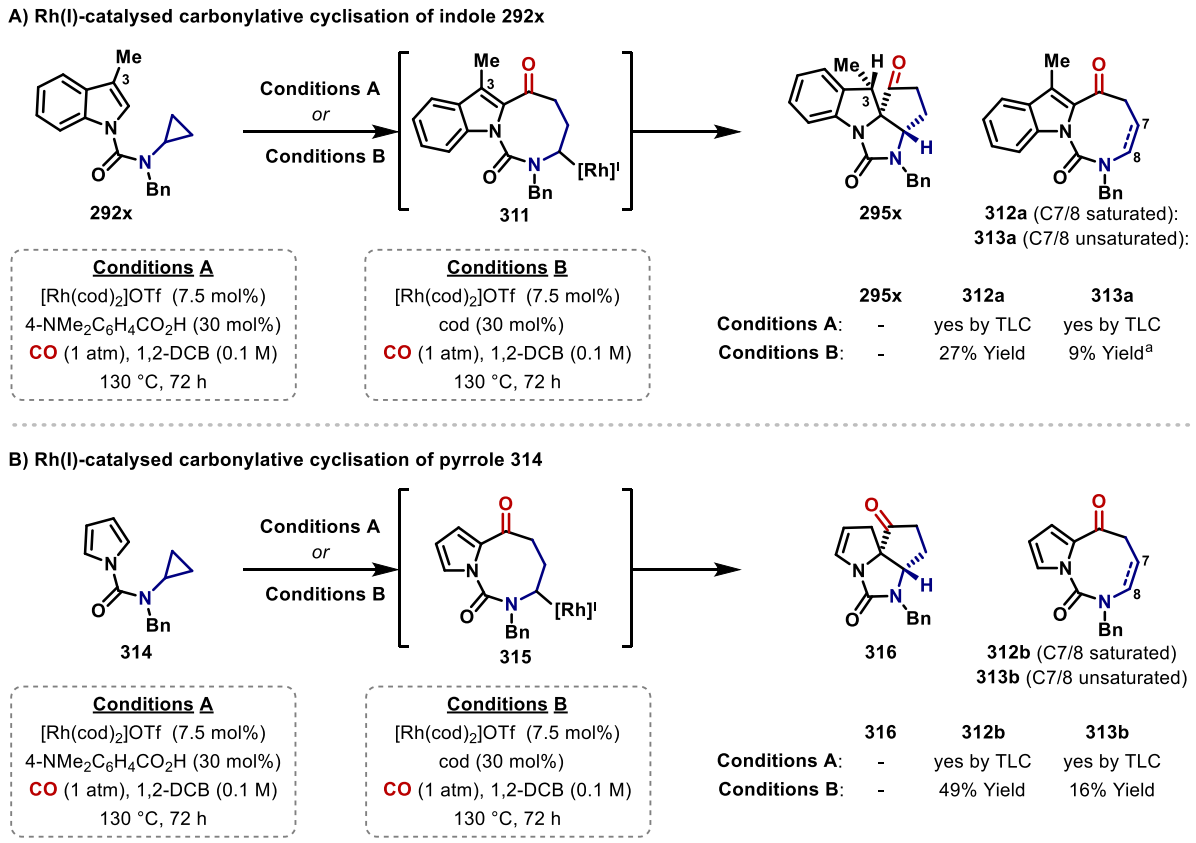


Table 18: Rh(I)-catalysed carbonylative C–C bond activation triggered *exo*-polycyclisations of *N*-carbamoyl indoles and pyrroles. [a] Synthesised by G.-W. Wang.

To shed more light on the impact of the heteroaromatic core on the preferred mode of cyclisation, methyl-substituted indole **292x** and pyrrole derivative **314** were prepared and evaluated under carbonylative conditions (Scheme 89). Exposure of **292x** and **314** to the [Rh(cod)$_2$]OTf/4-$NMe_2C_6H_4CO_2H$ catalyst system resulted in the formation of trace quantities of 8-membered *N*-heterocycles **312a**/**313a** and **312b**/**313b**, as determined by TLC analysis. The corresponding indole/pyrrole dearomatised products **295x**/**316** were not observed. The formation of heterocycles **312a** and **312b** is consistent with the C–C bond forming sequence proposed for polycycle **295a** (*i.e.* C(sp^2)–C(sp^2) reductive elimination from intermediate **296** is favoured over C(sp^2)–C(sp^3) reductive elimination, see Scheme 82). Compared with the counterpart indole-based systems **292a–o** (*cf.* Table 16), the inability of indole **292x** and pyrrole **314** to undergo dearomative polycyclisation is not surprising. In the case of methyl-substituted indole **292x**, presumably the C-3 methyl group inhibits carbometallation of the indole C2–C3 π-system; consequently, terminating protodemetallation or β-hydride elimination from alkyl-Rh(I)-intermediate **311** are favoured. Likewise, given that indole adducts undergo dearomatisation more readily than pyrrole variants, due to their stabilising benzenoid ring,[197-199] the deviation in reaction outcome of pyrrole derivative **314** is not unexpected. Partial optimisation of the cyclisation of pyrrole **314** to heterocycle **312b** was achieved by performing the reaction under phosphine and acid free conditions. Using these modifications, C7/8 saturated heterocycle **312b** was formed in 49% yield, with 3:1 selectivity over unsaturated adduct **312b** (conditions B, Scheme 89B). The [Rh(cod)$_2$]OTf/cod catalyst system also improved the yield of C7/8 saturated heterocycle **312a** to 27% (conditions B, Scheme 89A). In contrast to the studies outlined previously in this chapter and in Chapter 2, it is remarkable that these transformations proceed in the

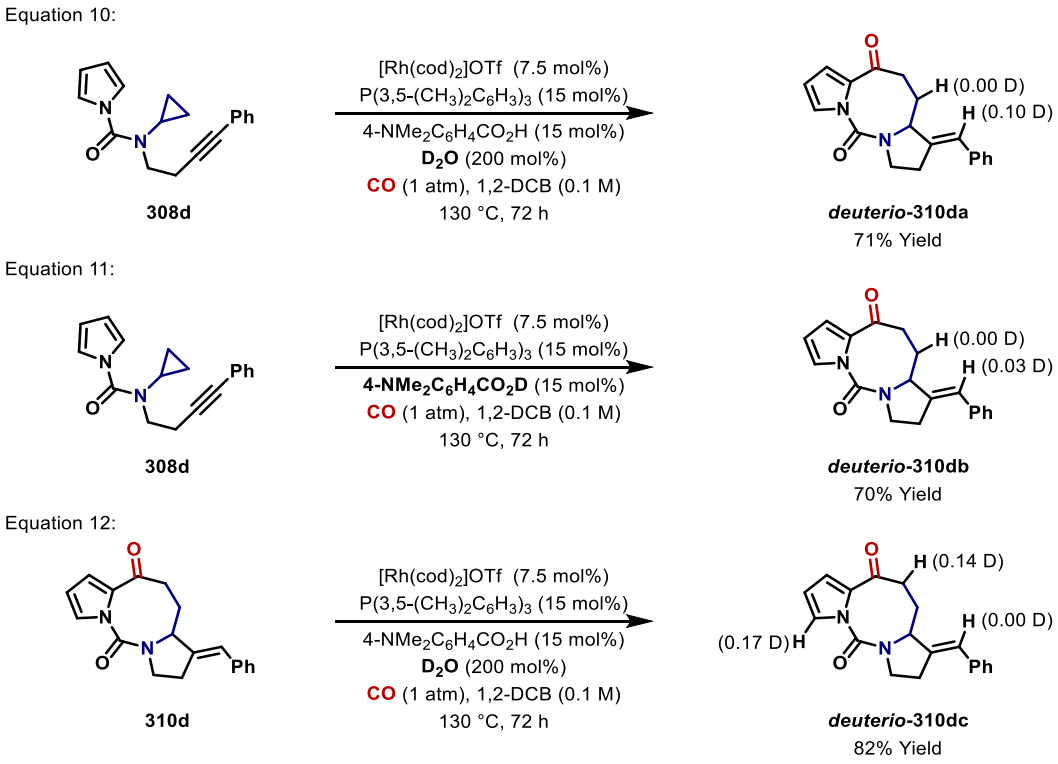
absence of an acid additive (*cf.* Table 2 and Table 15). Due to other successful research avenues, no further optimisation studies into either of these transformations was conducted.



Scheme 89: Evaluation of indole **292x** and pyrrole **314** in the Rh(I)-catalysed carbonylative cyclisation protocol. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

4.4.2 Deuterium exchange experiments

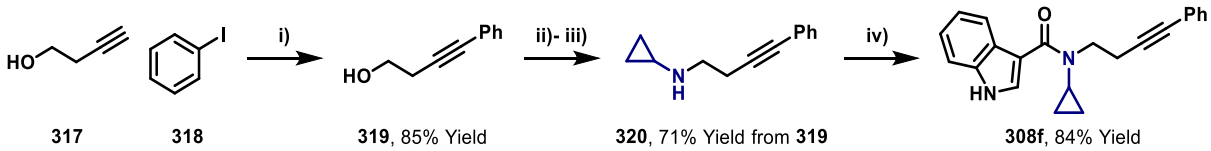
During the development of the *exo*-polycyclisation cascade, a series of mechanistic experiments were conducted to provide evidence for the proposed *syn*-carbometallation step (Scheme 90). Specifically, when the cyclisation of pyrrole derivative **308d** to polycycle **310d** was run in the presence of D_2O (300 mol%), deuterium incorporation was detected only at the vinylic C–H position (10% D) of ***deuterio*-310da** (Equation 10). This observation is consistent with the formation of the second ring occurring *via* a *syn*-carbometallation-protodemetallation sequence from an intermediate related to **309** (*cf.* intermediate **306**, Scheme 87). Likewise, when the cyclisation of **308d** to **310d** was performed in the presence of 15 mol% 4-$NMe_2C_6H_4CO_2D$ (prepared by dissolving 4-$NMe_2C_6H_4CO_2H$ in d_4-methanol and concentrating *in vacuo* three times) deuterium incorporation was observed at the vinylic C–H position (3% D) of ***deuterio*-310db** (Equation 11). Finally, as a control experiment, pure cyclised product **310d** was re-subjected to carbonylative conditions in the presence of D_2O (200 mol%). Analysis of recovered ***deuterio*-310dc** revealed no exchange at the vinylic position, thereby confirming that deuterium exchange occurs during but not after product formation.



Scheme 90: Mechanistic experiments.[a] [a] Equation 10 was conducted by G.-W. Wang.

4.4.3 Extension to further classes of polycyclisation cascade

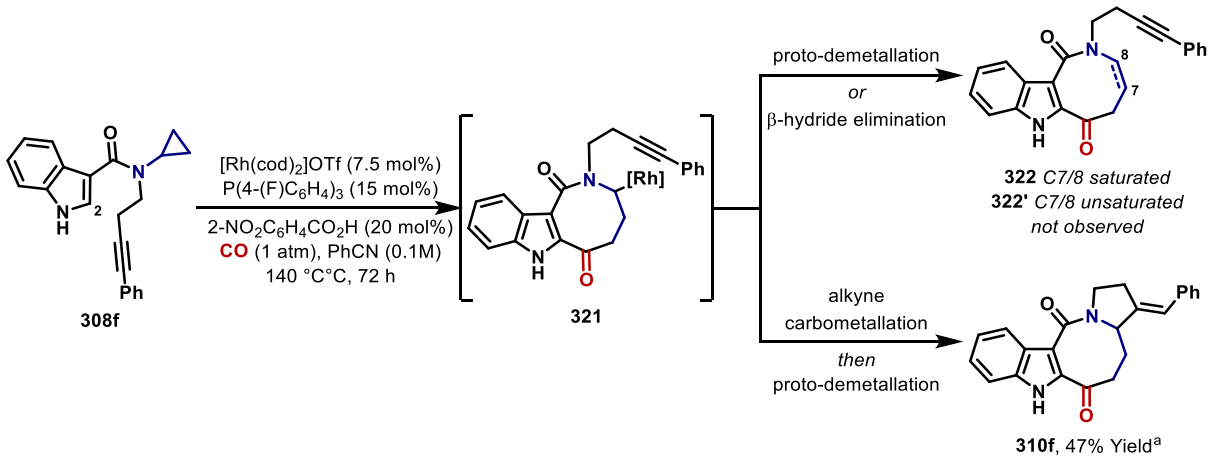
With a rationale in hand for the generation of 8,5-fused polyheterocycles **310a**–**e**, it was anticipated that additional processes should be achievable by exploring the scope of the nucleophilic component. In particular, we were interested in examining the suitability of heteroaromatic C3- and C2-cyclopropylamides bearing tethered alkyne units. As discussed previously in Chapter 2, heteroarenes were identified as excellent carbon nucleophiles in the Rh(I)-catalysed "capture-collapse" heterocyclisations of aminocyclopropanes to target 8-membered *N*-heterocycles. To validate this idea, C3-carbamoyl indole **308f** bearing a pendant alkyne motif was readily synthesised in a four-step process (Scheme 91). Following a known procedure, Sonogashira coupling of alkyne **317** with 2-iodoaniline **318** delivered alcohol **319** in 85% yield.[210] Conversion of alcohol **319** to its corresponding tosylate and subsequent displacement with cyclopropylamine afforded amine **320**. Next, EDCI-mediated coupling of amine **320** and indole-1*H*-3-carboxylic acid provided cyclopropylamide **308f** in 84% yield.



Scheme 91: Synthesis of C3-carbamoyl indole **308f**.[a] *Reagents and conditions*: i) $PdCl_2(PPh_3)_2$, CuI, Et_3N, 65 °C, 12 h, 85%; ii) tosyl chloride, DMAP, Et_3N, CH_2Cl_2, 0°C, 1 h, 85%; iii) cyclopropylamine, CH_3CN, 0 °C to 90 °C,

16 h, 85%; iv) 1*H*-indole-3-carboxylic acid, EDCI, DMAP, CH_2Cl_2, r.t., 18 h, 84%. [a] Compounds **320** and **308f** were synthesised by G.-W. Wang.

With substrate **308f** in hand, attention turned to the critical Rh(I)-catalysed carbonylative polycyclisation protocol (Scheme 92). When approaching this transformation, our primary concern was if the catalytically generated alkyl-Rh(I)-intermediate **321** could be coaxed into a second C–C bond-forming process (**321** to **310f**) *or* if it would be prone to undergo immediate protodemetallation/*β*-hydride elimination to give 8-membered heterocycles **322**/**322'**. Pleasingly, under modified carbonylative conditions ([Rh(cod)$_2$]OTf (7.5 mol%), P(4-FC_6H_4)$_3$ (15 mol%), 2-$NO_2C_6H_4CO_2H$ (20 mol%) in PhCN), 8,5-fused polyheterocycle **310f** was generated in 47% yield and 8-membered heterocycles **322**/**322'** were not observed. The preferential formation of polyheterocycle **310f** is most likely due to the highly coordinating nature of the alkyne tether, which outcompetes protodemetallation/*β*-hydride elimination from alkyl-Rh(I)-intermediate **320**, and hence enables the second annulation.



Scheme 92: Rh(I)-catalysed carbonylative C–C bond activation triggered *exo*-polycyclisation of indole **308f**. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

The yield of polyheterocycle **310f** was improved by increasing the loading of 2-$NO_2C_6H_4CO_2H$ to 100 mol%; using this modification polyheterocycle **310f** was generated in 62% yield (Table 19A). Encouraged by the success of this strategy, further substrate scope involving alternative C-3 and C-2 carbamoyl heteroarenes was evaluated alongside G.-W. Wang (Table 19). Extension to pyrrole (**308g**–**h**), furan (**308i)** and thiophene (**308j**) nucleophiles provided **310g**–**j** with similar levels of efficiency (Table 19A). Additionally, complementary *exo*-polycyclisations involving metallation of the C-3 position of heteroarenes were also effective, leading to 8,5-polyheterocycles **310k**–**n** in 43–67% yield (Table 19B). By blocking the C-2 position, pyrrole **308o** was able to cyclise *via* the C-4 position, affording **310o** in 40% yield (Table 19C).

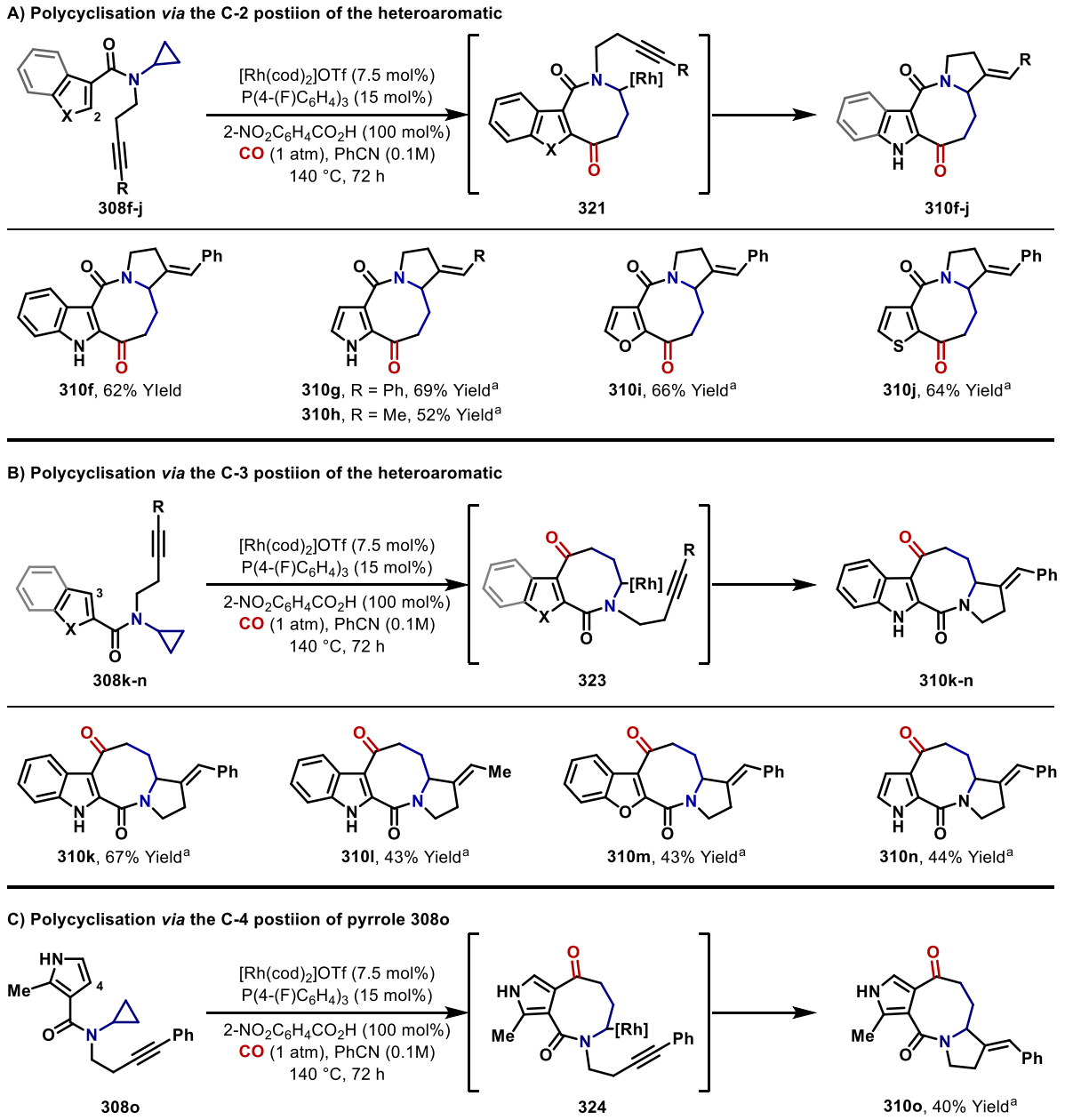


Table 19: Carbonylative C–C bond activation triggered *exo*-polycyclisations. [a] The corresponding substrate **308** and catalysis product **310** were synthesised by G.-W. Wang.

For completeness and to further illustrate the synthetic utility of the *exo*-polycyclisation strategy, additional results obtained by G.-W. Wang are highlighted in Table 20. Notably, other types of bond formation can be incorporated into these cascades; for example, nitrogen nucleophiles can be exploited in the formation of the first ring. For instance, cyclopropylurea **308p** underwent carbonylative *exo*-polycyclisation to deliver 7,5-polycycle **310p** in 73% yield (Table 20A). Compared to the processes outlined in Tables 18 and 19, this example is unique because the reductive elimination step generates a C–N bond rather than a C–C bond and, in addition to this deviation, a 7-membered ring is formed instead of an 8-membered ring. Even more impressively, the carbonylative cyclisation of pyrrole **308q**

bearing a 1,3-diene tether, proceeded to deliver 8,7-fused ring system **310q** in 36% yield as a single diastereomer (Table 20B). In this example, the formation of the 8-membered ring most likely occurs by a similar pathway to that outlined earlier (*cf.* intermediate **321**, Table 19A); however, the formation of the 7-membered ring is most easily rationalised *via* a hydrometallation pathway.[211,212] Specifically, it was proposed that protonation of the requisite alkyl-Rh(I) intermediate to Rh(III)-hydride **325** is followed by hydrometallation of the pendant 1,3-diene to give a Rh-π-allyl intermediate. From here, subsequent C–C reductive elimination affords polyheterocycle **310q**.

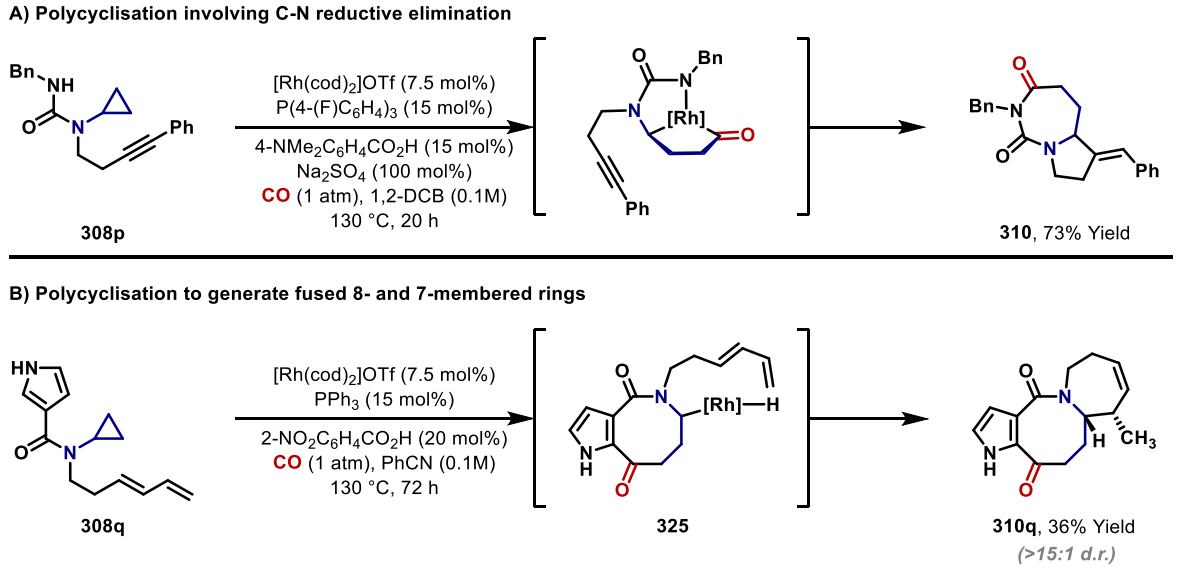


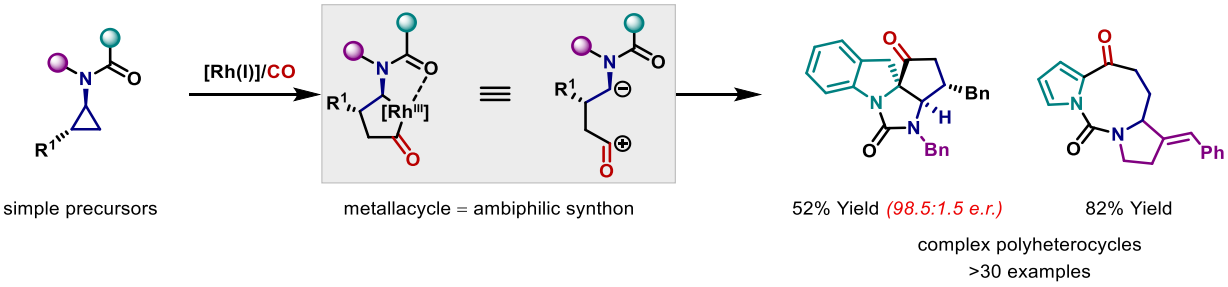
Table 20: Carbonylative C–C bond activation triggered *exo*-polycyclisations.[a] [a] The corresponding substrate **308p-q** and catalysis product **310p-q** were synthesised by G.-W. Wang.

On balance, the newly developed Rh(I)-catalysed carbonylative *exo*-polycyclisation of aminocyclopropanes exhibits broad compatibility and versatility with respect to the nucleophilic and electrophilic components. Notwithstanding these achievements, attempts by G.-W. Wang to use less nucleophilic arenes (*e.g. N*-benzoyl) for the first ring formation were unsuccessful (*cf.* Scheme 51). Equally, efforts to access 8,6- or 7,6-fused polyheterocycles by inserting an additional methylene linker in the alkyne tether were also met with failure, and so too was the replacement of the alkyne unit with alternative π-unsaturated units (*e.g.* an alkene or allene). Despite these drawbacks, a major advantage of this protocol is its robust nature, a characteristic reflected by the ease with which polyheterocycles **310a**–**q** are produced in a single-step from relatively simple precursors.

4.5 Summary and Conclusion from the studies in Chapter 4

Alongside G.-W. Wang, it has been shown that rhodacyclopentanones can be successfully employed to achieve multifaceted polycyclisation cascades. Our method capitalises on the ambiphilic nature of rhodacyclopentanones to construct two new ring systems of a diverse array of polycyclic targets that are difficult-to-access by conventional methods. This aspect is exemplified by the development of a

unique indole dearomatisation protocol and polycyclisations that incorporate challenging medium ring formations. For the former, deuterium exchange experiments and DFT experiments (conducted by T. Young) are consistent with a mechanistic pathway involving C(sp^2)–C(sp^2) reductive elimination (*i.e.* **296** to **293**, Scheme 82) and stereoretentive protodemetallation of alkyl-Rh(I) species **298**. By applying the knowledge acquired from these studies, it was discovered that related alkyl-Rh(I) intermediates (*i.e.* **309**/**321**/**323**/**324**) could be repurposed and exploited to engage with pendant π-unsaturated units to form a diverse collection of 8,5-, 7,5-, and 8,7-fused polyheterocycles. This proof-of-concept study highlights how catalytic C–C bond activation can be harnessed for the design and synthesis of complex and unusual molecular scaffolds that ultimately lie in underexplored regions of chemical space.



Scheme 93: Rh(I)-catalysed carbonylative C–C bond activation triggered polycyclisations.

Chapter 5 – The total synthesis of conolidine and the formal synthesis of apparicine

5.1 Introduction

In Chapter 2, the discovery and development of a general platform to generate heteroarene fused 8-membered *N*-heterocycles by Rh(I)-catalysed carbonylation of cyclopropylamides was successfully accomplished. Accordingly, it was envisioned that this methodology could be showcased and applied in the total synthesis of conolidine. Chapter 5 describes the successful realisation of this concept and its implementation as part of a general strategy to access members of the monoterpenoid indole alkaloid family.

5.1.1 The isolation and biological activity of conolidine, apparicine and related indole alkaloids

Monoterpenoid indole alkaloids constitute the largest class of tryptamine-derived alkaloids found in nature.[213,214] These compounds are of paramount importance due to their broad range of biological activities and diverse structural topologies.[215] Accordingly, many of these alkaloids have and continue to gain prominence as attractive targets for chemical synthesis.[216-218] Among them, is a small subclass known as the C5-nor stemmadenine natural products. The first alkaloid of this class to be reported was (-)-apparicine, which was isolated from *Aspidosperma dasycarpon* in 1965 (Figure 3).[219] The structural elucidation of apparicine revealed an indole fused bicyclic ring system, consisting of an 8-membered C-ring and a piperidine D-ring. A nitrogen atom resides at one of the bridgehead positions and an *E*-exocyclic trisubstituted alkene moiety is found at C20.[220] Over 20 monoterpenoid indole alkaloids structurally related to apparicine have been discovered, and as indicated by the framework in Figure 3, they are unified structurally by an indole fused azabicyclo[4.2.2]decane core (highlighted in blue). Representative molecules from this intriguing alkaloid family include (+)-conolidine,[221] (+)-ervaticine,[222] (-)-apparicine-21-one,[223] (*Z*)-vallesamine,[224,225] alstoniascholarine A,[226] 16(*S*) -hydroxyl-16,22-dihydroapparicine,[225] schloraisine N,[227] and more highly functionalised alkaloids such as taberhaine D,[228] (+)-alstonamine,[229,230] angustilobine C[231] and angustilobine A.[232]

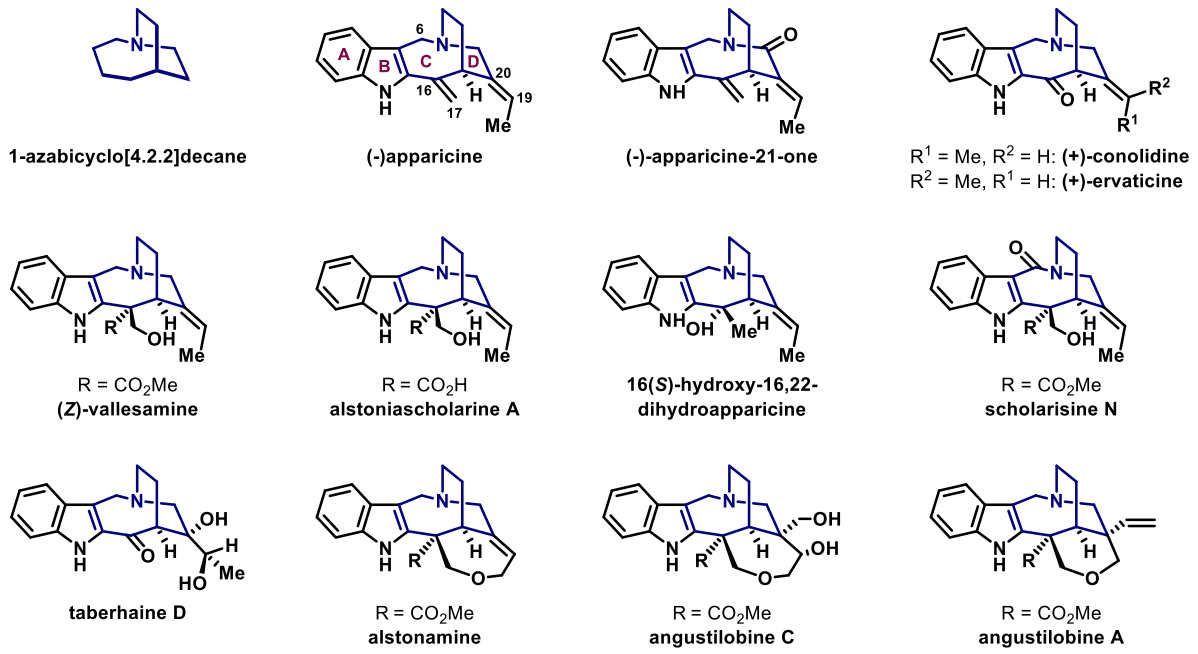


Figure 3: Structure of conolidine, apparicine and related alkaloids. Biogenetic numbering is shown on (-)-apparicine.

The C5-nor stemmadenine family are of great interest to the scientific community due to their promising pharmacological value. Investigations have shown that some members exhibit remarkable biological activities such as antimicrobial,[233,234] antibacterial[235] and opioid[236,237] properties. More specifically, investigations into the medicinal properties of conolidine have revealed that it is an effective non-opioid analgesic for persistent pain.[237] Additionally, these studies demonstrated that both enantiomers of conolidine possess similar *in vivo* activities with comparable potency to morphine.[237] Furthermore, conolidine has served as a structural platform for the identification of synthetic analogues, with recent medicinal chemistry programmes identifying molecules DS39201083 and DS54360155 as more potent analgesics *in vivo* (Figure 4).[238,239] However, the exact mode of action of conolidine and these compounds remains unclear. Additionally, the low natural abundance of conolidine (conolidine was isolated in just 0.00014% from the stem bark of *Tabernaemontana divaricata*[221]) and the scarcity of chemical approaches to access the azabicyclo[4.2.2]decane skeleton have hindered investigations into the potential therapeutic properties of conolidine and related C5-nor stemmadenine natural products.

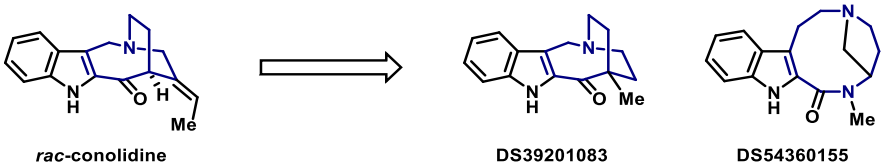
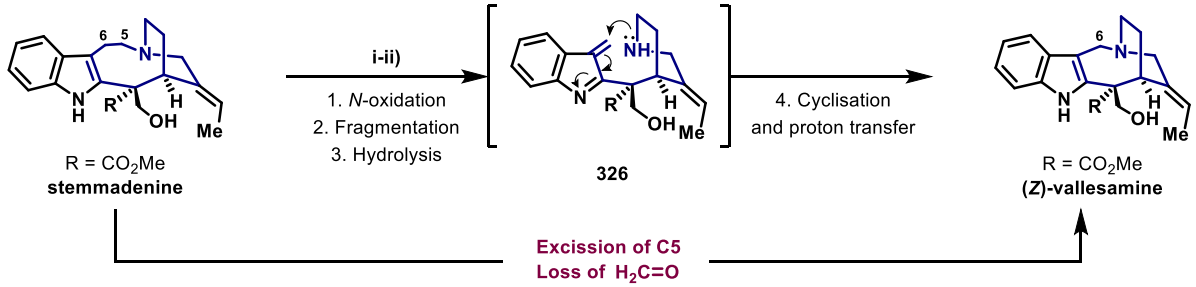


Figure 4: Medicinally important synthetic analogues of conolidine.

C5-nor stemmadenine natural products are biogenetically defined by the presence of only one carbon (C6) connecting the indole C3-position to the aliphatic nitrogen atom. This unusual structural

scaffold is a consequence of C5 excision from the original two-carbon tryptamine bridge of the alkaloid stemmadenine (Scheme 94). In the biosynthesis of C5-nor stemmadenine compounds, the excision of the C5 carbon is proposed to be promoted by *N*-oxidation of the bridgehead nitrogen atom.[221] This proposal has been validated chemically through the conversion of stemmadenine to its C5-nor analogue (*Z*)-vallesamine (Scheme 94).[240] In this example, excision of the C5 carbon occurs by a sequence of (1) *N*-oxidation of the aliphatic nitrogen atom, (2) fragmentation which results in the loss of the C5 carbon as formaldehyde, (3) hydrolysis and (4) cyclisation through intermediate **326** to afford (*Z*)-vallesamine.[240-242]



Scheme 94: Biomimetic semi-synthesis of (*Z*)-vallesamine from stemmadenine. *Reagents and conditions*: i) H_2O_2; ii) $(CF_3CO)_2O$, -5 °C *then* dilute aqueous NaOH.

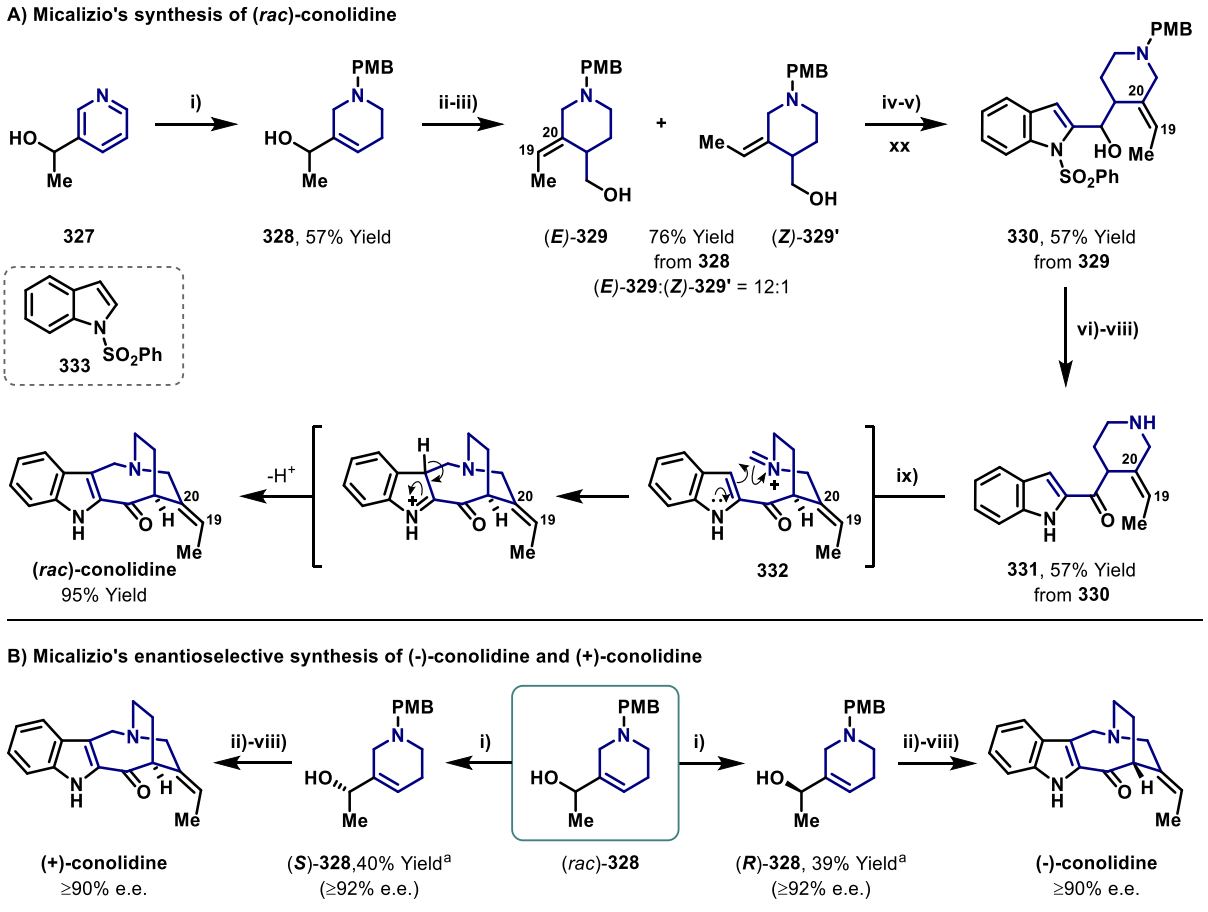
5.1.2 Previously reported total synthesis of conolidine

In recent years, conolidine, apparicine and related alkaloids have garnered increased attention from synthetic chemists due to their structural complexity coupled with their attractive biological activities. Arguably, the greatest synthetic challenge in the synthesis of these alkaloids resides in the formation of the strained azabicyclo[4.2.2]decane skeleton (*highlighted in blue throughout*) and stereochemical control of the exocyclic trisubstituted alkene unit. The total synthesis of conolidine and apparicine have been accomplished by five research groups and the following section aims to summarise previous strategies to these challenging targets.

5.1.2.1 Micalizio's total synthesis of (*rac*)-conolidine and (+)-conolidine and (-)-conolidine

The first total synthesis of (*rac*)-conolidine was disclosed by Micalizio and co-workers in 2011 (Scheme 95). Their synthetic route was inspired by the proposed biosynthetic conversion of stemmadenine to (*Z*)-vallesamine (*cf.* Scheme 94), and provided (*rac*)-conolidine in 9 steps in an overall yield of 18%.[237] The synthesis began with *N*-alkylation of pyridine **327** and subsequent hydride reduction with $NaBH_4$ to afford **328** in 57% yield. A [2,3]-Still-Wittig rearrangement of allylic alcohol **328** was then utilised to establish the desired alkene geometry at C19–C20. This was achieved by the conversion of **328** to its corresponding tributylstannylmethyl ether, which was then treated with *n*-BuLi to give (*E*)-**329** ((*E*)-**329**:(*Z*)-**329'** = 12:1). Dess-Martin periodinane mediated oxidation of (*E*)-**329** to the corresponding β,γ-unsaturated aldehyde and nucleophilic addition of 2-lithio-benzenesulfonyl-indole **333** provided a

mixture of stereoisomeric alcohols **330**, which was readily converted to keto **331** in an additional three-step sequence. For the final transformation, Micalizio took advantage of a conformationally-controlled intramolecular Mannich cyclisation to incorporate the final C–C bond of the natural product. This was accomplished by reacting **331** with formaldehyde in the presence of TFA. The reaction is believed to proceed through cyclisation intermediate **332**, which structurally resembles that of intermediate **326** in the biomimetic synthesis of vallesamine (*cf.* **332** *v.s.* **326**, see Scheme 94). Intermediate **332** underwent spontaneous intramolecular cyclisation to install the strained 1-azabicyclo[4.2.2]decane core, thereby completing the total synthesis of (*rac*)-conolidine. The execution of this reaction not only facilitated the total synthesis, but also underscores how chemical innovation can be prompted by inspiration from nature. In addition, using this synthetic approach, either enantiomer of conolidine could be assessed *via* enzymatic resolution of alcohol **328** (Scheme 95B). The authors were able to confirm the absolute configuration of naturally occurring conolidine (known as (+)-conolidine) and its unnatural enantiomer (known as (-)-conolidine) in 10 synthetic steps from commercially available starting material **327**.

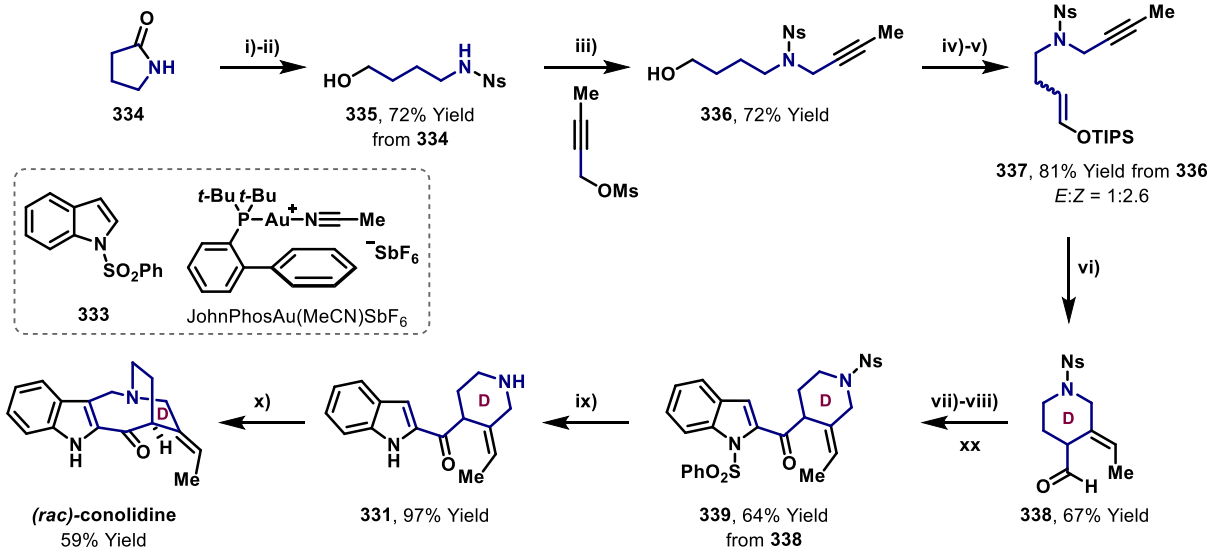


Scheme 95: Micalizio's total synthesis of conolidine. A) *Reagents and conditions (some details were not provided by the authors)*: i) 4-methoxybenzyl chloride, 1,2-dichloroethane, reflux, 8 h *then* $NaBH_4$, MeOH, 0 °C to r.t., 57%; ii) KH, Bu_3SnCH_2I, THF, r.t., 4 h; iii) *n*-BuLi, THF, -78 °C to 0 °C, 1 h, 76% from **328**, *Z*:*E* (**329**:**329'**) = 12:1; iv) Dess-Martin periodinane, CH_2Cl_2/H_2O; v) *n*-BuLi, indole **333** *then* keto **329**, THF, -78 °C, 1 h; vi) sodium amalgam, r.t., 4 h; vii) MnO_2, CH_2Cl_2, r.t., 3 h; viii) α-chloroethyl chloroformate, 1,2-dichloroethane,

84 °C, 4 h, 43% from **330**; ix) CF_3CO_2H, $(CH_2O)_n$, CH_3CN, reflux, 2 h, 95%, yield reported is for the preparation of the ½ H_2SO_4 salt of (*rac)*-conolidine. B) *Reagents and conditions (some details were not provided by the authors)*: i) vinyl acetate, amano lipase PS, hexane, 4Å MS, 30 °C, 18 h, 40% (*S*)-**328** and 39% (*R*)-**328**; ii) KH, Bu_3SnCH_2I, THF, r.t., 4 h; iii) *n*-BuLi, THF, -78 °C to 0 °C, 1 h; iv) CH_2Cl_2, DIPEA, DMSO, SO_3-Pyr, -10 °C to 0 °C, 1 h, 99%; v) *n*-BuLi, 1-(phenylsulfonyl)indole **333**, THF, -78 °C, 1 h; vi) sodium amalgam, r.t., 4 h; vii) MnO_2, CH_2Cl_2, r.t., 3 h; viii) α-chloroethyl chloroformate, 1,2-dichloroethane, 84 °C, 4 h; viii) CF_3CO_2H, $(CH_2O)_n$, CH_3CN, reflux, 2 h, 95%, yield reported is for the preparation of the ½ H_2SO_4 salt of (+)-conolidine. [a] Yield reported is for after hydrolysis.

5.1.2.2 Takayama's total synthesis of (*rac*)-conolidine

In 2016, Takayama reported an alternative 10-step synthesis of (*rac*)-conolidine with 11% overall yield (Scheme 96).[243] Initially, 2-pyrrolidinone **334** was elaborated to alcohol **336** in a three-step sequence. From here, alcohol **336** was oxidised and transformed into silyl enol ether **337** as a mixture of geometrical isomers ((*E*)-**337**:(*Z*)-**327** = 1:2.6). Next, after extensive investigation, a Au(I)-catalysed 6-*exo*-dig cyclisation assembled the piperidine D-ring and secured the exocyclic (*E*)-ethylidene appendage. The authors commented that employment of electrophilic JohnPhosAu(MeCN)SbF_6 (Echavarren catalyst[244]) and the judicious inclusion of H_2O as a proton source were essential for the reaction to proceed. Utilising these conditions, piperidine **338** was obtained in 67% yield, compared to 19% in the absence of H_2O. Nucleophilic addition of 2-lithio-benzenesulfonyl-indole **333** and oxidation of the resulting secondary alcohol with Dess-Martin periodinane afforded ketone **339** in 64% yield from **338**. To complete the synthesis, removal of both *N*-protecting groups provided known intermediate **331**, and using modified conditions reported by Micalizio, an acid mediated Mannich cyclisation delivered (*rac*)-conolidine in 59% yield.

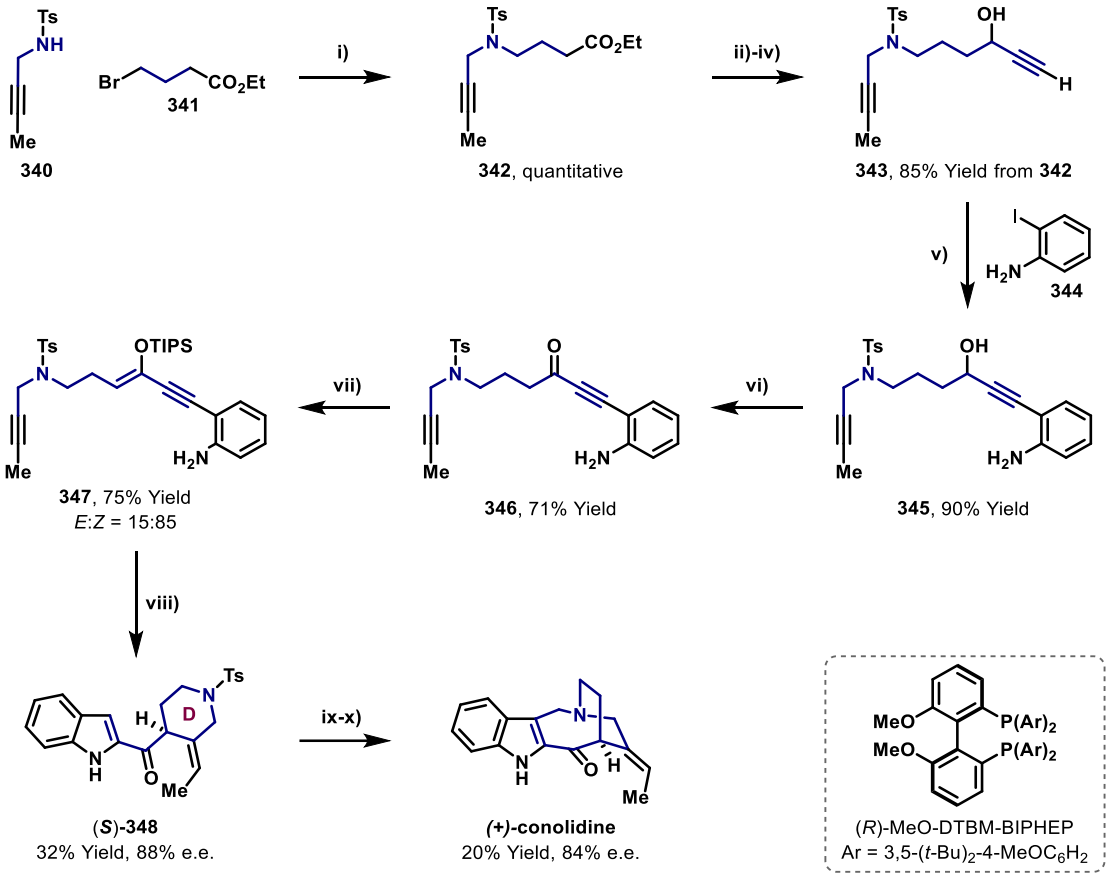


Scheme 96: Takayama's total synthesis of (*rac*)-conolidine. *Reagents and conditions*: i) *n*-BuLi, NsCl, THF, -78 °C, 22 h, 85%; ii) $NaBH_4$, THF/H_2O (10:1), 0 °C to r.t., 12 h; iii) K_2CO_3, DMF, 50 °C, 72%; iv) IBX,

DMSO, 50 °C, 1.5 h; v) TIPSOTf, Et_3N, CH_2Cl_2, 0 °C, 5h, 81% from **336**, *E*:*Z* = 1:2.6; vi) JohnPhosAu(MeCN)SbF_6, CH_2Cl_2, H_2O, 0 °C, 12 h, 67%; vii) *n*-BuLi, 1-(phenylsulfonyl)indole **333**, THF -78 °C then **338**, 6 h; viii) DMP, CH_2Cl_2, 0 °C to r.t., 1.5 h, 64% from **338**; xi) 1M KOH, MeOH, reflux *then* PhSH, r.t., 97%; x) CSA, $(CH_2O)_n$, CH_3CN, reflux, 59%.

5.1.2.3 Fujii's total synthesis of (+)-conolidine

Simultaneously with the disclosure from Takayama's group, Fujii and co-workers published a closely related synthesis of (+)-conolidine (Scheme 97). Their approach also featured a Au(I)-cyclisation step to construct the piperidine D-ring, in addition to the indole unit. Their route delivered (+)-conolidine in 10 steps in an overall yield of 3% and 84% e.e. (Scheme 97).[245] The synthesis commenced with alkylation of tosylamine **340** with ethyl 4-bromobutanoate **341** which proceeded in quantitative yield to give intermediate **342**. Successive treatment of **342** with DIBAL and 1,2-addition of lithium (trimethylsilyl)acetylide, followed by desilylation with TBAF delivered terminal alkyne **343** in good yield. Sonogashira coupling of alkyne **343** with 2-iodoaniline **344** provided alkynylaniline **345** in 90% yield. Oxidation of **345** with MnO_2 to keto **346**, followed by treatment with TIPSOTf furnished silyl enol ether **347** as the substrate for the ensuing key Au(I)-catalysed cyclisation reaction. Inspired by conditions developed in the Toste lab,[246] treatment of conjugated enyne **347** with (*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$/$AgSbF_6$ in toluene afforded cyclised product **348**, albeit in a modest 32% yield but with 88% e.e. In agreement with Takayama's report, the fortuitous inclusion of water was critical for this transformation.[243] Additionally, studies demonstrated that the desired cyclised product **348** could only be formed from the sterically less hindered *Z*-isomer of **347** (the *Z* and *E* isomers of **347** could be separated by column chromatography). From **348**, cleavage of the *N*-tosyl protecting group with sodium/naphthalene, and finally Micalizio's acid mediated Mannich reaction provided (+)-conolidine in 34% yield with 84% enantiopurity.

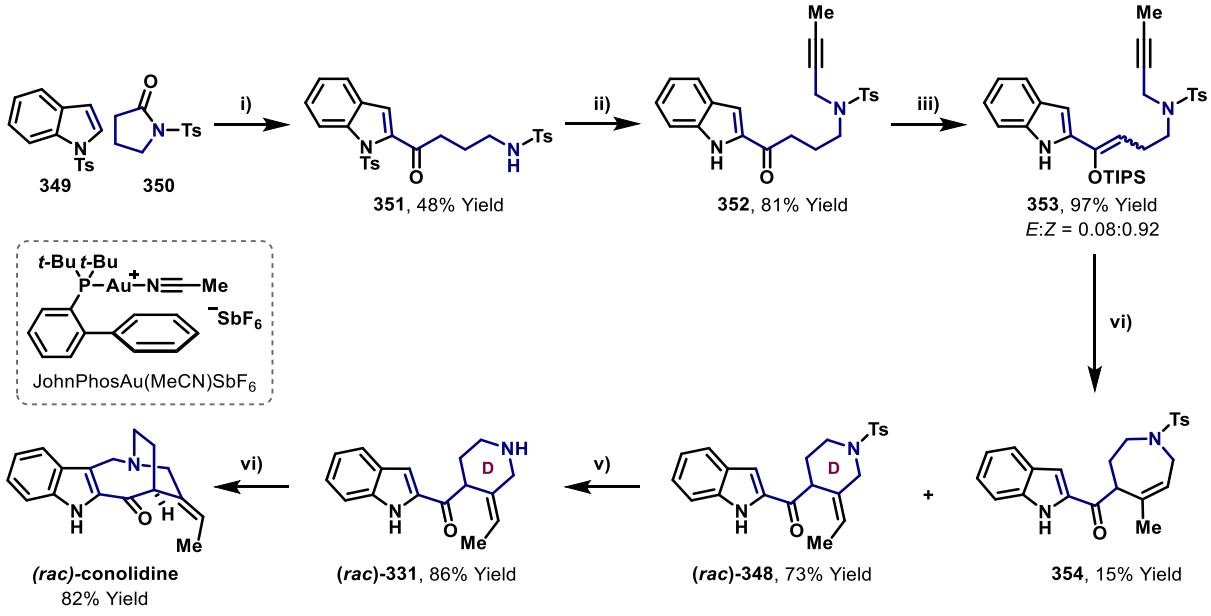


Scheme 97: Fujii's total synthesis of (+)-conolidine. *Reagents and conditions*: i) NaH, DMF, r.t., 3 h, quantitative; ii) DIBAL, CH_2Cl_2, -78 °C, 1 h; iii) *n*-BuLi, trimethylsilylacetylene, -78 °C, 2h, 90% yield from **342**; iv) TBAF, THF, r.t., 1 h, 94%; v) 2-iodoaniline **344**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, CH_3CN, r.t., 1.5 h, 90%; vi) MnO_2, $CHCl_3$, reflux, 0.5 h, 71%, vii) TIPSOTf, Et_3N, CH_2Cl_2, -78 °C to r.t., 2 h, 75%, *E*:*Z* = 15:85; viii) (*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$, $AgSbF_6$, PhMe, r.t., 10 min *then* (*Z*)-**347**, r.t., 17 h, 32%, 88% e.e.; ix) Na/naphthalene, THF, 0 °C, 60%; x) CF_3CO_2H, $(CH_2O)_n$, CH_3CN, reflux, 5 h, 34%, 84% e.e..

5.1.2.4 Qi's total synthesis of (*rac*)-conolidine

Recently, Qi and co-workers reported a conceptually similar synthesis of (*rac*)-conolidine (Scheme 98, *cf.* Schemes 96 and 97).[247] However, and more significantly, their route involves no non-strategic redox manipulations and remains the shortest route to date. Their 6-step synthetic route commenced with treatment of *N*-tosylindole **349** with *n*-BuLi, followed by addition of *N*-tosylpyrrolidone **350** provided ketone **351** in 48% yield. Next, a one-pot *N*-alkylation of **351** and selective deprotection of the *N*-indole-tosyl group afforded alkynyl ketone **352** in 81% yield. Ketone **352** was then readily converted to silyl enol ether **353** (*E*:*Z* = *0*.08:0.92). Like Takayama and Fujii, Qi also opted for a Au(I)-catalysed cyclisation to form the piperidine D-ring and to secure the *E*-geometry of the exocyclic double bond. DFT calculations revealed that an unprotected indole unit was essential for the Au(I)-catalysed cyclisation to proceed. Additionally, the group reported that the use of [JohnPhosAu(CH_3CN)]SbF_6 in toluene favoured the formation of the desired 6-*exo*-dig product **348** (73% yield) over the 7-*endo*-dig

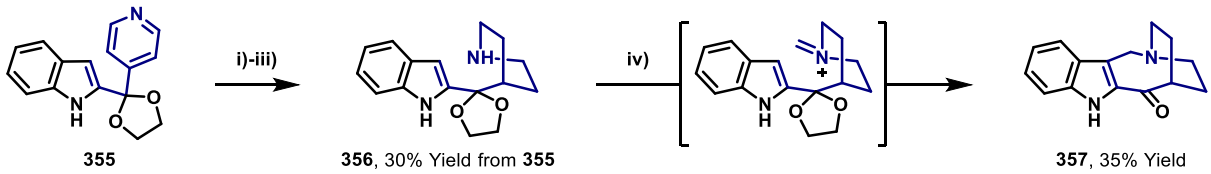
product **354** (15% yield). Compared to Fujii's route (Scheme 97), ketone **348** could be accessed in just 4 steps. The remainder of the synthesis was accomplished by removal of the *N*-tosyl group to provide piperidine ketone **331**, and finally using the conditions identified by Micalizio, an acid promoted Mannich reaction of **331** afforded (*rac*)-conolidine in 82% yield.



Scheme 98: Qi's total synthesis of (*rac*)-conolidine. *Reagents and conditions*: i) *n*-BuLi, THF, -78 °C, 5 min *then* *N*-tosylpyrrolidone **350**, -30 °C to -15 °C, 4 h, 48%; ii) K_2CO_3, 1-bromo-2-butyne, CH_3CN, 80 °C, 16 h *then* TBAF, 35 °C, 16 h, 81%; iii) TIPSOTf, 2,6-lutidine, 35 °C, 97%, *E*:*Z* = 0.08:0.92; iv) [JohnPhosAu(CH_3CN)]SbF_6, H_2O, PhMe, 60 °C, 2 h, 73% for **348**, 15% for **354**; v) Na/naphthalene, THF, -78 °C, 86%; vi) CF_3CO_2H, $(CH_2O)_n$, CH_3CN, reflux, 2 h, 82%.

5.1.3 Previously reported total synthesis of apparicine

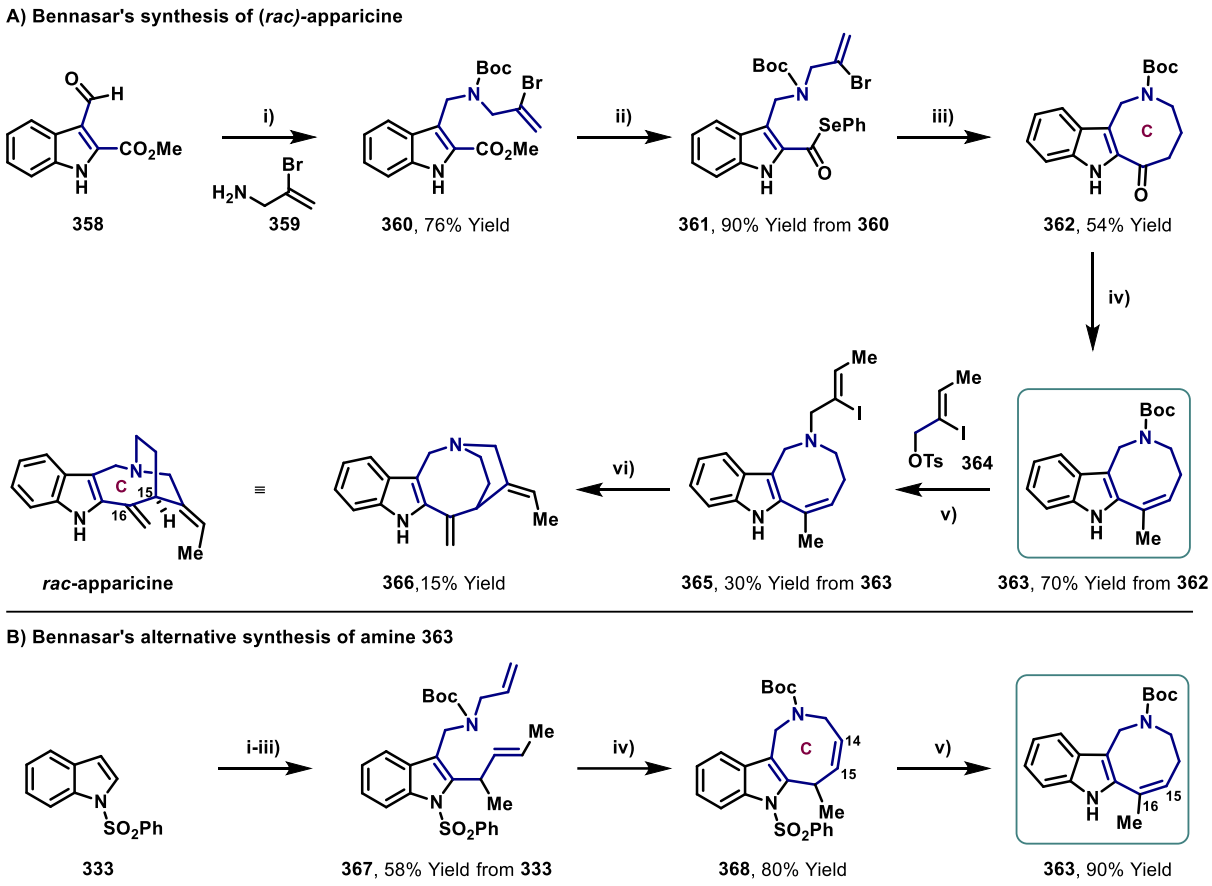
As stated previously, conolidine and apparicine share an intriguing azabicyclo[4.2.2]decane architecture and are distinguishable by the choice of substituent at C16 (see Figure 3). Apparicine has also been the subject of previous synthetic studies; however, due to reactivity and selectivity issues this alkaloid remained an elusive target. In the late 1970s, Joule and co-workers developed an approach which allowed for the construction of the bicyclic skeleton of apparicine (*i.e.* azocane **357**, Scheme 99).[248] Their approach centred on an acid promoted Mannich reaction between acetal **356** and formaldehyde, which after removal of the keto protecting group, afforded bicycle **357** in 35% yield (Scheme 99). However, the total synthesis of apparicine was not disclosed/completed at this time. It would take a further 40 years until Micalizio successfully utilised an acid mediated Mannich transformation to construct the azazbicyclo[4.2.2]decane core of related conolidine with the requisite *E*-exocyclic alkene appendage at C20 (see Scheme 95).



Scheme 99: Joule's Approach to the apparicine skeleton. *Reagents and conditions (some details were not provided by the authors)*: i) benzyl bromide, EtOAc, reflux, 5 h; ii) $NaBH_4$, MeOH, 10 °C; iii) H_2, Pd/C, MeOH, r.t., 16 h, 30% from **355**; iv) acetic acid, $(CH_2O)_n$, r.t., 4.5 h *then* aqueous HCl, 24 h, 35%.

5.1.3.1 Bennasar's total synthesis of (*rac*)-apparicine

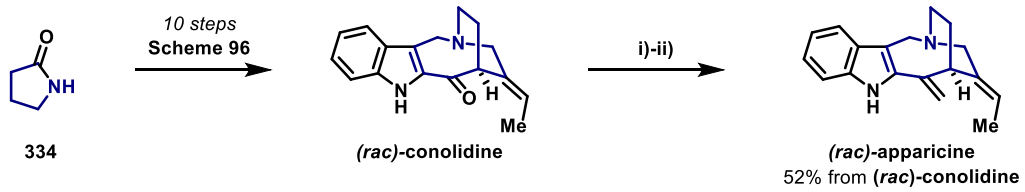
Following Joule's initial studies (and before Micalizio's synthesis of conolidine), Bennasar and co-workers disclosed the first total synthesis of (*rac*)-apparicine in 2009 (Scheme 100).[249,250] The authors developed a two-pronged approach to form the 8-membered C-ring. One approach entailed an acyl radical cyclisation followed by ketone-alkene function group interconversion (Scheme 100A). This was accomplished *via* reductive amination of aldehyde **358** with 2-bromo-2-propenylamine **359**, followed by Boc protection of the resulting secondary amine. From here, ester **360** was advanced to selenoester **361** in a two-step sequence. Treatment of selenoester **361** with *n*-Bu_3SnH and Et_3B initiated a radical cyclisation that constructed the 8-membered ring of azocane **362** in 54% yield. Finally, 1,2-addition of MeLi and subsequent dehydration under acidic conditions secured amine **363**. Alternatively, the 8-membered C-ring could be formed by ring closing metathesis and base-induced isomerisation of the C–C double bond from C14–C15 to C15–C16 (Scheme 100B). This approach was achieved by the quick elaboration of indole **333** to **367** *via* a 3-step sequence. Subsequent treatment of indole **367** with Grubbs 2nd generation catalyst forged the 8-membered C-ring and produced amine **368** in 80% yield. Exposure of **368** to *t*-BuOK in refluxing THF simultaneously cleaved the *N*-indole protecting group and promoted alkene isomerisation to deliver amine **363** in 90% yield. Next, *N*-Boc deprotection and *N*-alkylation with tosylate **364** delivered amine **365** in 30% yield. The authors commented that, following Boc deprotection, the resulting secondary amine was highly susceptible to acid mediated decomposition. Finally, the synthesis was concluded by a cationic Pd(0)-catalysed Heck cyclisation of **365** which closed the piperidine ring and furnished (*rac*)-apparicine in 15% yield. Bennasar noted that the Heck-cyclisation was complicated by concomitant unravelling of the exocyclic alkylidene substituent which gave rise to unidentified side products, therefore contributing to the low overall yield of (*rac*)-apparicine.



Scheme 100: Bennasar's total synthesis of (*rac*)-apparicine. A) *Reagents and conditions*: i) 2-bromo-2-propenylamine **359**, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, r.t., overnight *then* Boc_2O, 1,4-dioxane, r.t., overnight, 76%; ii) LiOH, THF/H_2O *then* 1 M aq. HCl *then* Et_3N, Bu_3P, PhSeCl, r.t., overnight, 90%; iii) *n*-Bu_3SnH, Et_3B, PhH, r.t., 2 h, 54%; iv) MeLi, THF, -10 °C, 2 h *then* TsOH, CH_3CN, r.t., 2 h, 70%; v) 1 M aq. HCl, MeOH, r.t., 4.5 h *then* **364**, DIPEA, CH_2Cl_2/CH_3CN, r.t., 2 h, 30%; vi) $Pd(OAc)_2$, Ph_3P, Ag_2CO_3, PhMe, Et_3N, 80 °C, 1.5 h, 15%. B) *Reagents and conditions*: i) *n*-BuLi, THF, 0 °C, 2 h *then* CuCN, -78 °C to 0 °C, 2 h *then* (*E*)-4-chloro-2-pentene, -78 °C to r.t., 12 h, 85%; ii) Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, -78 °C, 4 h, 76%; iii) allylamine, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, r.t., overnight *then* Boc_2O, Et_3N, MeOH, reflux, 5 h, 90%; iv) Grubbs 2nd generation catalyst, CH_2Cl_2, reflux, 4.5 h, 80%; *t*-BuOK, THF, reflux, 48 h, 90%. Biogenetic numbering is shown on (*rac*)-apparicine.

5.1.3.2 Takayama's total synthesis of (*rac*)-apparicine

In conjunction with reporting the synthesis of (*rac*)-conolidine, Takayama simultaneously accomplished the synthesis of (*rac*)-apparicine.[243] To this end, lactam **334** was elaborated in 10 synthetic steps to afford (*rac*)-conolidine (Scheme 96). From here, 1,2-addition of MeLi to (*rac*)-conolidine provided the corresponding tertiary alcohol and subsequent dehydration with TFA gave (*rac*)-apparicine in 52% yield (Scheme 101).



Scheme 101: Takayama's total synthesis of (*rac*)-apparicine. *Reagents and conditions*: i) MeLi, THF, -78 °C, 1 h; ii) TFA, CH_2Cl_2, 0 °C to r.t., 5.5 h, 52%.

5.1.4 Summary of existing methods for the synthesis of conolidine, apparicine and related monoterpene indole alkaloids

Over the past decade, a renaissance of interest in conolidine and apparicine has led to several creative and instructive total synthesis being disclosed. Central to Micalizio's successful synthesis of conolidine, was clever inspiration from nature and exploratory studies by Joule to construct the 8-membered C-ring *via* an acid promoted Mannich cyclisation. However, all subsequent synthesis of conolidine have relied heavily on this biosynthetically inspired transformation to build the bridged azabicyclo[4.2.2]decane core, with yields fluctuating between 34% and 95%. Additionally, existing strategies still suffer from unsolved limitations including long step counts, inefficient or unselective transformations or lack of control of absolute stereochemistry. However, the most promising of all these synthetic routes was Qi's synthesis of (*rac*)-conolidine, which proceeded in only 6 steps. In contrast to Micalizio, Bennasar opted for a Pd(0)-catalysed Heck cyclisation to close the bridged ring system of apparicine; this transformation is highly challenging (the authors reported only a 15% yield) thereby reinforcing the notion that further improvements in synthetic efficiency are needed. To date, none of the other alkaloids of this class have been synthesised by synthetic chemists and this can perhaps be attributed to the highly strained bicyclic core. Therefore, to address the unmet synthetic challenges posed by conolidine and related indole alkaloids, investigations towards their synthesis were initiated and will be discussed in the following sections.

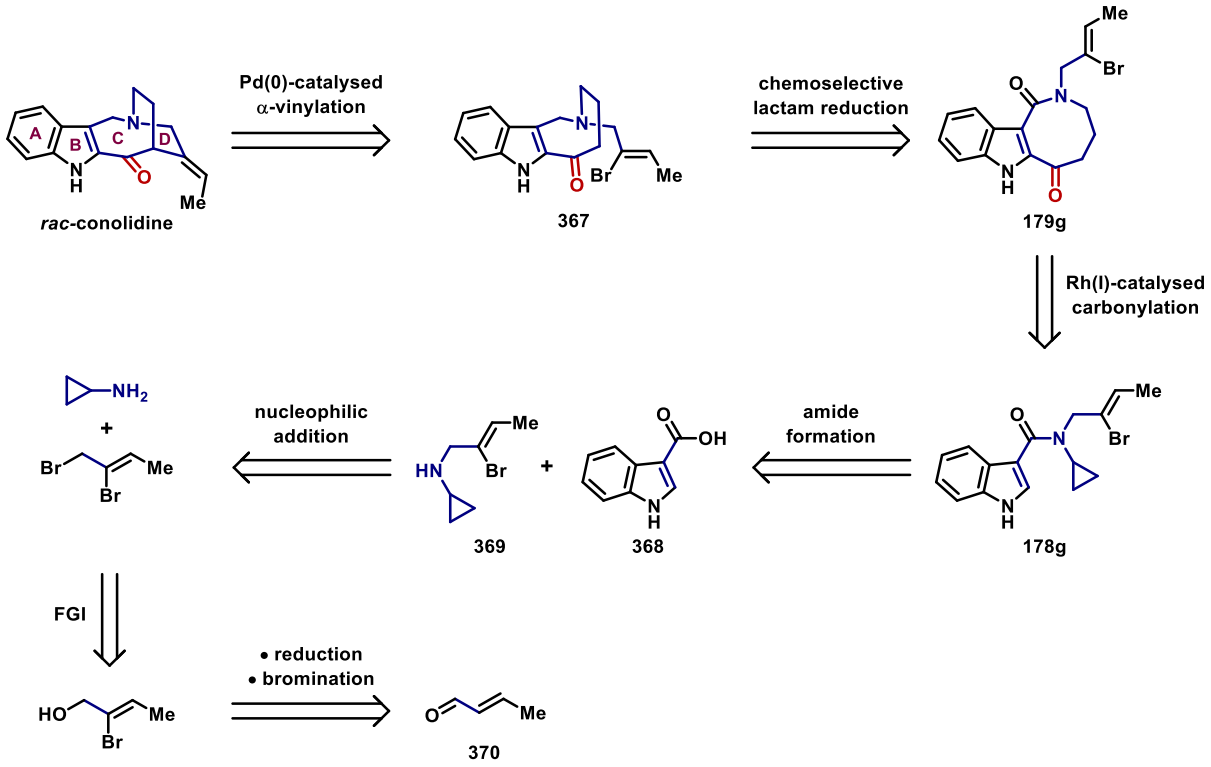
5.2 A Rh(I)-catalysed cyclisation approach towards the total synthesis of (*rac*)-conolidine

The considerations outlined above prompted attempts to develop a short and selective synthesis of C5-nor stemmadine alkaloids. The ideal synthesis would be redox and step economical and allow for a modular approach to some of the higher functionalised indole monoterpenoids (see Figure 3). With the ultimate goal of rendering the synthesis asymmetric, (*rac*)-conolidine was selected as the initial target.

5.2.1 First generation retrosynthetic analysis of (*rac*)-conolidine

The first generation retrosynthetic analysis of (*rac*)-conolidine is outlined in Scheme 102. The planned synthesis hinged on two key steps: Rh(I)-catalysed carbonylation to form the 8-membered C-ring and a Pd(0)-catalysed α-vinylation of a keto enolate to forge the nitrogen bridgehead. With this strategy in

mind, it was envisioned that the azabicyclo[4.4.2]decane scaffold would be assembled by late stage construction of the C15–C20 bond, which would also secure the *E*-exocyclic alkene geometry. Thus, conolidine would be accessed from vinyl halide **367** through a Pd(0)-catalysed enolate vinylation. Key intermediate **367** would derive from lactam **179g** *via* an ambitious chemoselective lactam reduction**.** In a second key retrosynthetic disconnection, it was anticipated that lactam **179g** would arise from amide **178g** *via* the newly developed Rh(I)-catalysed carbonylative ring expansion of cyclopropylamides outlined in Chapter 2. Amide **178g** would be obtained from acid **368** and amine **369**, which, in turn, could be formed by a known three-step sequence from *trans*-crotonaldehyde **370**.[251]



Scheme 102: First generation retrosynthetic analysis of (*rac*)-conolidine.

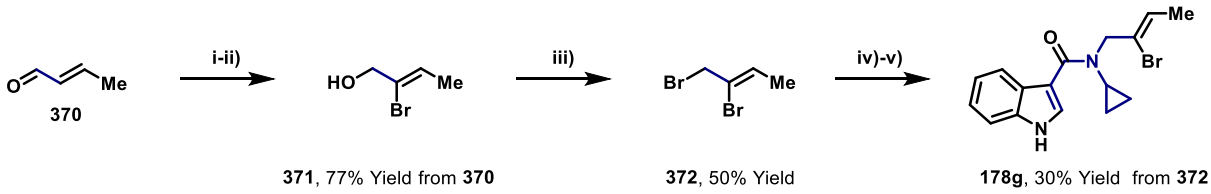
Several aspects of the retrosynthesis detailed in Scheme 102 warrant additional comment. Firstly, the carbonylative disconnection to form the 8-membered ring is highly productive because this transformation would construct the C-ring of conolidine in just six steps from simple starting materials. However, this strategy is not without significant risk, as the necessary survival of the vinyl bromide adds an additional layer of complexity. Secondly, whilst formidable advances in Pd(0)-catalysed reactions have been made, to the best of our knowledge, there are no reported α-vinylation reactions involving (aza)cyclooctane rings to produce bridged ring systems. Nevertheless, we were drawn to the prospect of transforming **367** directly to (*rac*)-conolidine, as it would represent a novel application of palladium catalysis for the construction of the azabicyclo[4.2.2]decane core. Literature precedence for this α-vinylation strategy will be presented in Section 5.2.4.5. Overall, the value of pursuing this particular strategy would be three-fold: (1) it would showcase the power of the Rh(I)-catalysed

cyclisation methodology to access 8-membered *N*-heterocycles; (2) it would allow rapid access to the 8-membered C-ring from relatively simple amide **178g**; and more significantly (3), if the Pd(0)-catalysed α-vinylation transformation could be rendered asymmetric then conolidine would be obtained in high enantiomeric purity.

5.2.1.1 Studies towards the carbonylative ring expansion of a *N*-vinyl bromide aminocyclopropane

Note: *The work in this section was carried out in collaboration with Mr. H. Lan, as part of his CDT rotation project at Bristol.*

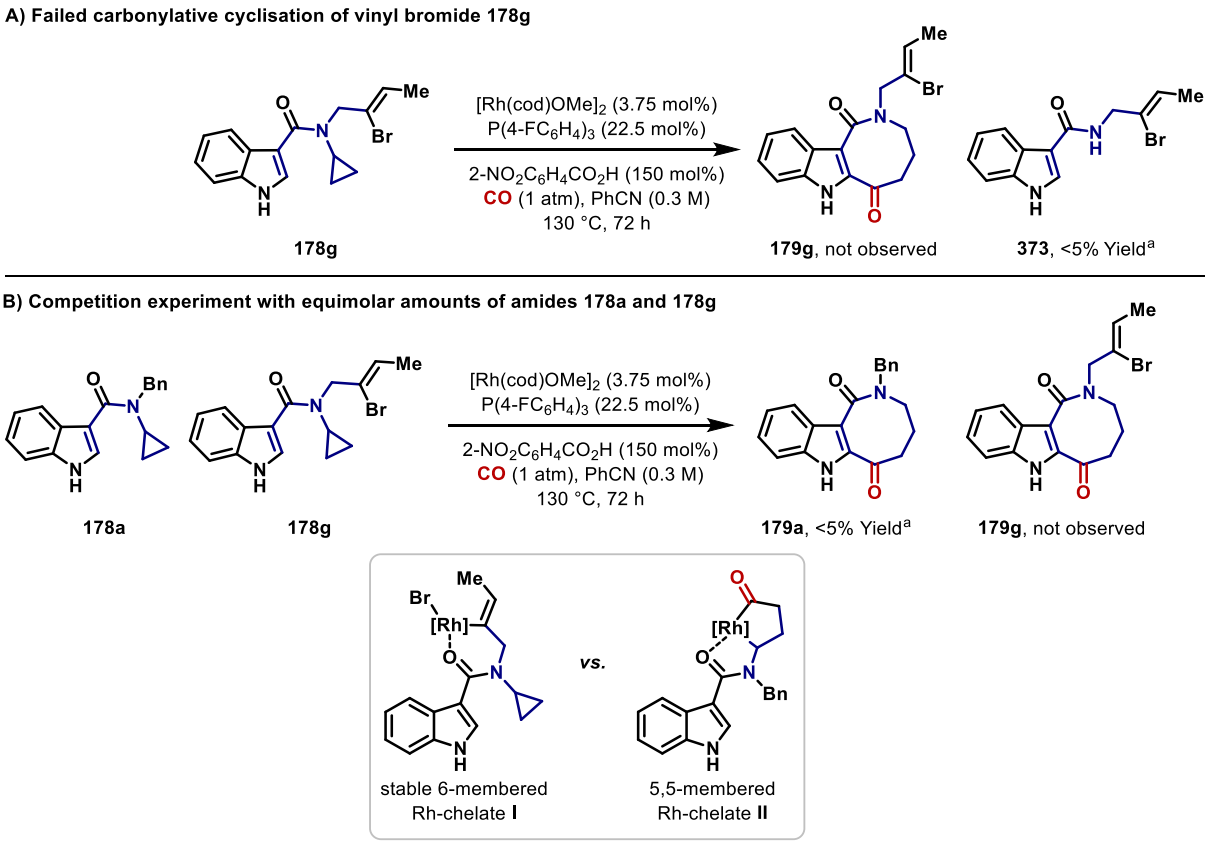
Initially, amide **178g** was prepared in a 5-step sequence as outlined in Scheme 103. Following a known procedure, successive treatment of *trans*-crotonaldehyde with bromine and Et_3N, followed by subsequent reduction with $NaBH_4$ delivered alcohol **371** in good yield.[251] This material was used without further purification and all of these steps were easily carried out on multi-gram scale. Conversion of alcohol **371** to its corresponding mesylate and subsequent displacement with LiBr, delivered dibromide **372**.[251,252] Next, *N*-alkylation of cyclopropylamine with **372** and addition of the ensuing amine to 1*H*-indole-3-carbonyl chloride under basic conditions provided amide **178g** in 46% yield. With substrate **178g** in hand, attention turned to the critical Rh(I)-catalysed carbonylative cyclisation.



Scheme 103: Synthesis of vinyl bromide **178g**. *Reagents and conditions* i) Br_2, CH_2Cl_2, 0 °C, 1 h *then* Et_3N, 0 °C to r.t., 1.5 h, 89%; ii) $NaBH_4$, THF/H_2O, 0 °C, 1 h, 86%; iii) MsCl, THF, -30 °C *then* LiBr, -30 °C to r.t., 50%; iv) aminocyclopropane, K_2CO_3, CH_3CN, 0 °C to r.t., 65%; v) 1*H*-indole-3-carboxylic acid, oxalyl chloride, cat. DMF, CH_2Cl_2, 0 °C, 1 h *then* **372,** Et_3N, CH_2Cl_2, 0 °C to r.t. 16 h, 46%. Compounds **372** and **178g** were synthesised by H. Lan.

Using the previously optimised conditions for parent substrate **178a** (see Section 2.5, Table 6), exposure of amide **178g** to $[Rh(cod)OMe]_2$/P-(4-$FC_6H_4)_3$/2-$NO_2C_6H_4CO_2H$ catalyst system, under an atmosphere of CO, was expected to result in the formation of lactam **179g**. However, rather than obtaining the desired product, analysis of the ^1H NMR spectrum of the crude reaction mixture indicated trace amounts of protodecyclopropanated **373** and unreacted **178g** (Scheme 104A). Side-product **373** was not isolated but was assigned based on comparison with NMR data of starting material **178g** and by analogy with observations in related processes (see Chapter 3, Scheme 67). As discussed previously, side-products akin to **373** most likely derive from hydrolysis of the corresponding enamide, which in

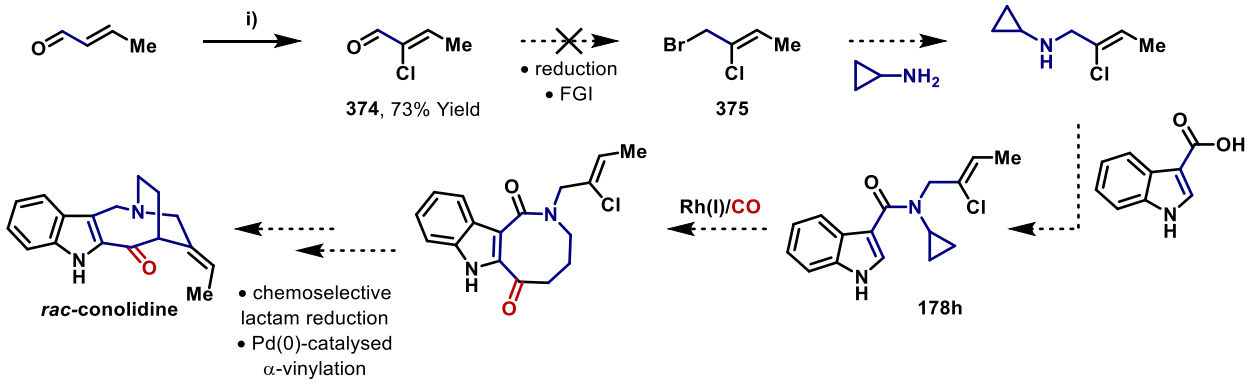
turn is generated by rhodacyclobutane decomposition. Subsequently, H. Lan evaluated key reaction parameters, such as catalyst ([Rh(cod)OMe]$_2$ *vs.* [Rh(cod)$_2$]OTf), phosphine ligand (electron-rich *vs.* electron-poor), acid additive (alternative benzoic acids *vs.* aliphatic acids) and temperature (120 °C *vs.* 130 °C *vs.* 140 °C). Unfortunately, the desired product **179g** was not formed under any of these conditions. From these experiments, it was proposed that the Rh(I)-catalyst was inserting preferentially into the C–Br bond of the *N*-vinyl bromide unit. To test this hypothesis, a competition experiment was performed in which equimolar amounts of amides **178a** and **178g** were subjected to the [Rh(cod)OMe]$_2$ carbonylative catalysis conditions. Consistent with our hypothesis, only trace amounts of cyclised product **179a** were observed in the ^{1}H NMR spectrum of the crude material. This result suggests that the Rh(I)-catalyst inserts preferentially into the C–Br bond and this unproductive reaction pathway outcompetes the desired C–C bond activation (*i.e.* rhodacyclopentanone formation). This can be rationalised by the relative stability of the corresponding 6-membered Rh(III)-chelate **I** compared to rhodacyclopentanone **II** (Scheme 104). As amide **178g** did not exhibit the desired activity, no further investigations into this transformation were conducted.



Scheme 104: Experiments conducted by H. Lan. [a] The yield was determined by ^{1}H NMR analysis using 1,4-dinitrobenzne as an internal standard.

Given that vinyl bromide **178g** was incompatible in the Rh(I)-catalysed carbonylative cyclisation, cyclopropylamide **178h** bearing a vinyl chloride unit was proposed as a workable

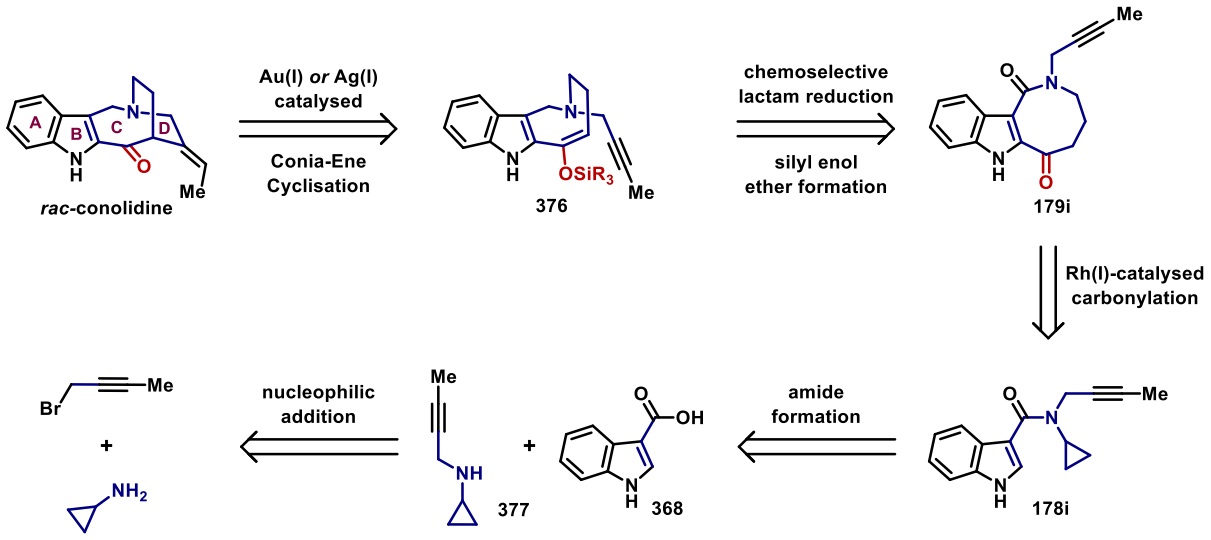
alternative. It is well established that C−Cl bonds undergo oxidative addition less readily with Rh(I)-catalysts compared to C−Br bonds.[253] However, vinyl chloride **178h** could not be accessed due to handling and volatility issues encountered during the conversion of aldehyde **374** to intermediate **375** (Scheme 105).[254]



Scheme 105: Attempted synthesis and application of vinyl chloride **178h**. *Reagents and conditions*: i) (diacetoxyiodo)benzene, pyridine hydrochloride, CH_2Cl_2, r.t., 73%.

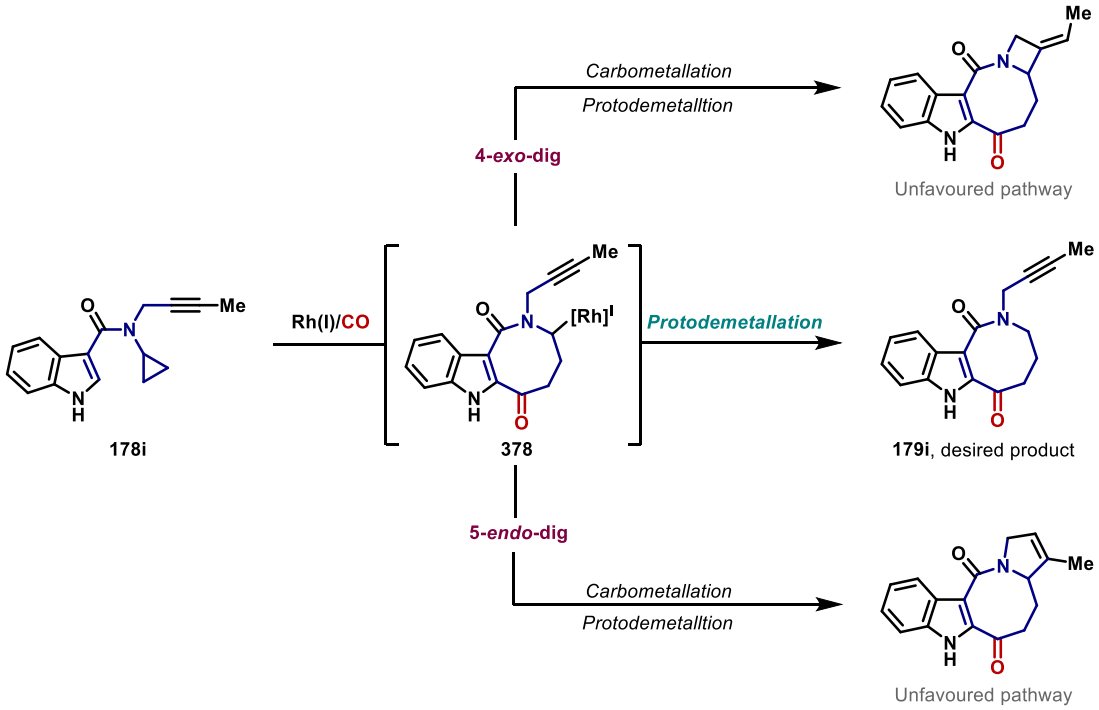
5.2.2 Second generation retrosynthetic analysis of (*rac*)-conolidine

Due to the unsuitability of vinyl bromide **178g** in the critical Rh(I)-catalysed carbonylative cyclisation reaction, the retrosynthetic analysis shown in Scheme 102 was re-evaluated. Specifically, carbonylative precursor **178g** was re-designed to include an alternative pre-installed *N*-functionalised appendage that would be amenable for subsequent construction of the piperidine D-ring. With this strategy in mind, the vinyl halide unit of **178g** was replaced with an alkyne component and the second generation retrosynthetic analysis of (*rac*)-conolidine is presented in Scheme 106. Taking inspiration from the groups of Li[255-257], Garg[258] and Takayama,[243] it was anticipated that the nitrogen bridgehead of (*rac*)-conolidine could be installed by a Au(I) or Ag(I)-catalysed[259] cyclisation of silyl enol ether **376**. The geometry of conolidine's trisubstituted exocyclic alkene would be defined by the *trans* alkyne activation mode of the Au(I) or Ag(I)-catalyst.[260] In turn, silyl enol ether **376** would arise from chemoselective lactam reduction and silyl ether formation of key late-stage compound **179i**, which would be accessed from amide **178i** using the Bower group's Rh(I)-catalysed carbonylation protocol. Finally, amide **178i** can be traced back to commercially available acid **368** and amine **377**, which can be readily derived from known compounds. The implementation of this strategy would not only serve to construct the 8-membered C-ring of (*rac*)-conolidine in just three steps, but would also avoid wasteful *N*-functionalisation steps at a later step in the synthesis.



Scheme 106: Second generation retrosynthetic analysis of (*rac*)-conolidine.

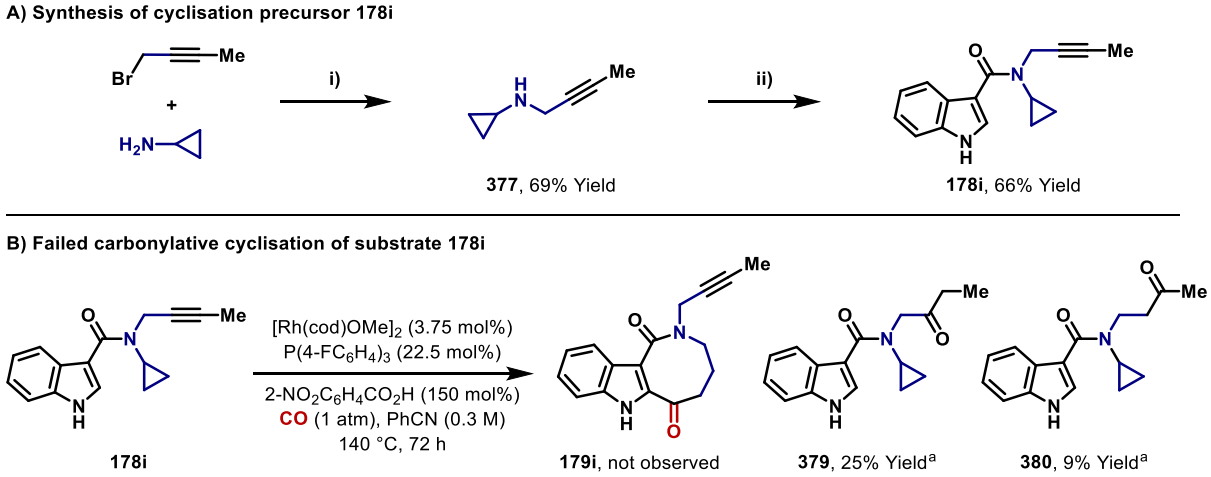
When considering the feasibility of substrate **178i** in the Rh(I)-catalysed carbonylation reaction, a notable concern was whether the catalytically generated Rh(I) intermediate (*i.e.* **378**, Scheme 107) would be trapped by the tethered alkyne (for related processes see Chapter 4). However, we remained optimistic that the alkyne moiety would remain intact for two reasons. Firstly, polycyclisation *via* a 4-*exo*-dig cyclisation mode would afford highly strained 8,4-fused heterocyclic products; therefore, this pathway was considered unfavourable. Secondly, as detailed in Section 4.4, no products arising from a 5-*endo*-dig pathway had been detected from structurally similar substrates.



Scheme 107: Rationale for suitability of substrate **178i** in Rh(I)-catalysed carbonylative cyclisation.

5.2.2.1 Studies towards the carbonylative ring expansion of a *N*-propargyl aminocyclopropane

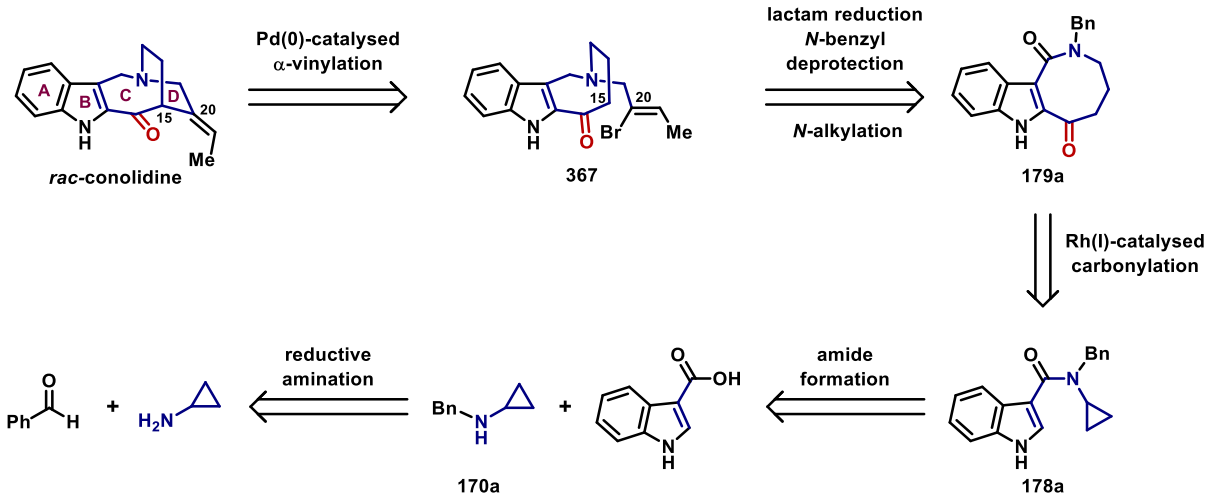
Following the retrosynthetic plan outlined in Scheme 106, the synthesis commenced with the scalable preparation of catalysis substrate **178i** (Scheme 108). *N*-Alkylation of aminocyclopropane with 1-bromobut-2-yne provided propargylic amine **377** in 69% yield. Next, addition of amine **377** to 1*H*-indole-3-carboxylic acid smoothly furnished amide **178i** in 66% yield. Attention then focussed on the crucial Rh(I)-catalysed carbonylative cyclisation. Disappointingly, efforts were thwarted, with alkyne hydration observed as a severe side reaction (Scheme 108B). Attempts to suppress this deleterious pathway by the inclusion of sodium sulfate or 4 Å molecular sieves as a drying agent, were also unsuccessful. Li has previously commented that transformations involving propargylic amine appendages routinely suffer from undesired hydration pathways.[256] However, as the reaction requires a balloon of CO, it is difficult to exclude all sources of adventitious water. Additionally, strong coordination of the alkyne component of **178i** to the Rh(I)-catalyst may prevent directed insertion into the cyclopropyl unit of **178i**. A brief survey of reaction components in the presence and absence of *either* sodium sulfate *or* 4 Å molecular sieves was undertaken. These parameters included Rh(I)-source ($[Rh(cod)OMe]_2$ *vs*. $[Rh(cod)_2]OTf$), representative phosphine ligands ($P(4\text{-}FC_6H_4)_3$ *vs*. PPh_3 *vs*. $P(4\text{-}OMeC_6H_4)_3$ *vs*. BINAP) and alternative acid additives ($2\text{-}NO_2C_6H_4CO_2H$ *vs*. fumaric acid *vs*. AdCOOH). Unfortunately, these efforts were ineffective with alkyne hydration remaining the predominant reaction pathway. Thus, efforts to access the 8-membered C-ring of conolidine with a pre-installed amide nitrogen group had again been foiled. Consequently, work on this substrate was abandoned and an amide nitrogen protecting group was sought.



Scheme 108: A) *Reagents and conditions* i) CH_3CN, 0 °C to r.t., 16 h, 69%; ii) 1*H*-indole-3-carboxylic acid, oxalyl chloride, cat. DMF, CH_2Cl_2, 0 °C, 1 h *then* **377**, Et_3N, CH_2Cl_2, 0 °C to r.t. 4 h, 66%. [a] The yield was determined by ^1H NMR analysis using 1,4-dinitrobenzne as an internal standard.

5.2.3 Third generation retrosynthetic analysis of (*rac*)-conolidine

Despite the setbacks discussed above, we returned to the primary task of completing the total synthesis of (*rac*)-conolidine. The greatest synthetic challenge encountered so far was identifying a suitable substrate for the Rh(I)-catalysed carbonylative cyclisation that contained a pre-installed *N*-functionalised appendage. In consideration of these challenges, it was decided to construct the 8-membered C-ring with a benign substituent on the amide nitrogen and then introduce the problematic *N*-vinyl bromide component. It was rationalised that the most expediate and logical approach was to revert to parent substrate **178a**, which possesses a *N*-benzyl group. A revised third generation retrosynthetic analysis of (*rac*)-conolidine is presented in Scheme 109.



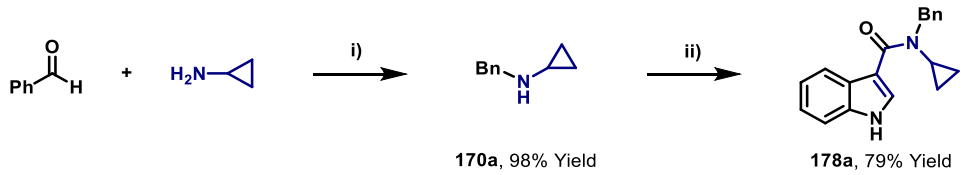
Scheme 109: Third generation retrosynthetic analysis of (rac)-conolidine.

Identical to the first generation strategy, it was anticipated that the C15–C20 bond would be constructed by Pd(0)-catalysed enolate coupling of vinyl bromide **367**. However, key late-state compound **367** would be accessed from cyclised lactam **179a** through a series of transformations including lactam reduction, *N*-benzyl deprotection and *N*-alkylation to install the vinyl bromide unit. In turn, lactam **179a** would arise from amide **178a** under the Rh(I)-catalysed carbonylative cyclisation protocol developed in Chapter 2. Amide **178a** would be derived from 1*H*-indole-3-carboxylic acid and amine **170a**, the latter of which would be derived from cyclopropylamine and benzaldehyde. Although previous studies have already demonstrated access to cyclised compound **179a** (see Section 2.5), the opportunity to evaluate a scalable synthetic route to this key intermediate was undertaken.

5.2.3.1 Further optimisation of Rh(I)-catalysed carbonylative cyclisation of cyclopropylamides

Cyclisation substrate **178a** was available in multigram quantities by a two-step procedure as outlined in Scheme 110. Reductive amination of benzaldehyde with cyclopropylamine afforded amine **170a** in excellent yield.[16] EDCI coupling of amine **170a** and 1*H*-indole-3-carboxylic acid delivered amide **178a**

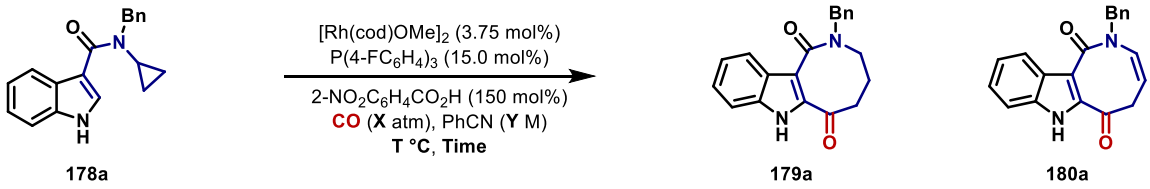
in 79% yield. With a large quantity of **178a** in hand, the Rh(I)-catalysed carbonylative cyclisation was re-examined.



170a, 98% Yield **178a**, 79% Yield

Scheme 110: Preparation of amide **178a**: *Reagents and Conditions*: i) $NaHCO_3$, MeOH, reflux, 16 h *then* cool to 0 °C, $NaBH_4$, 16 h, 98%; ii) 1*H*-indole-3-carboxylic acid, EDCI, DMAP, CH_2Cl_2, r.t., 12 hours, 79%.

As discussed in Section 2.5, the carbonylative cyclisation of **178a** was readily accomplished in 58% yield using 3.75 mol% $[Rh(cod)OMe]_2$ in combination with 22.5 mol% of $P(4\text{-}FC_6H_4)_3$ and 150 mol% $2\text{-}NO_2C_6H_4CO_2H$ in PhCN at 130 °C. During these original studies, carbonylative reactions were performed on 0.15 mmol (0.5 mL) scale using a balloon of CO. Therefore, in order to facilitate studies on the remaining transformations, investigations were directed towards increasing the scale of the reaction and transferring the protocol to a sealed reactor vessel, for example the ChemSCAN II®, which would allow for the rapid screening of reaction conditions in parallel and on a larger scale (limited by a reaction volume of 5 mL). A selection of key results are given in Table 21.



178a **179a** **180a**

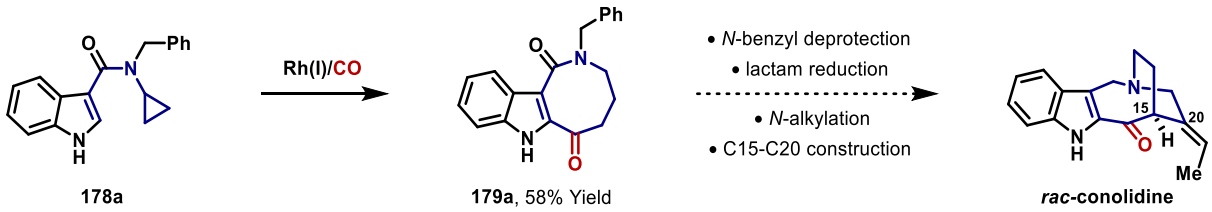
Entry	Scale	X	Y	T °C	Time	Remaining 178a[a]	Yield 179a[a]	Yield 180a[a]
1[b]	0.15 mmol	1	0.3	130 °C	72 h	-	58%	4%
2	1.50 mmol	1	0.3	130 °C	24 h	23%	10%	-
3	1.00 mmol	2	0.3	130 °C	24 h	14%	31%	trace
4	1.00 mmol	2	0.3	120 °C	24 h	yes by TLC	25%	trace
5	**1.00 mmol**	**3**	**0.3**	**130 °C**	**24 h**	**-**	**45%**	**6 %**
6	1.00 mmol	3	0.3	120 °C	24 h	yes by TLC	18%	trace
7	1.00 mmol	4	0.3	130 °C	24 h	-	31%	11%
8	1.00 mmol	4	0.3	120 °C	24 h	-	30%	3%
9	1.00mmol	3	0.2	130 °C	24 h	-	33%	7%
10	1.50 mmol	3	0.5	130 °C	24 h	-	31%	4%

Table 21: Evaluation of conditions for carbonylative cyclisation of **178a** using a ChemSCAN II® reactor. [a] Yields of isolated products unless stated otherwise. [b] A balloon of CO and 22.5 mol% of $P(4\text{-}FC_6H_4)_3$ was used.

In order to directly compare the effect of the CO delivery method on the yield of **179a**, a side-by-side comparison of a balloon of CO *vs*. 1 bar of CO in a ChemScan II® reactor was first examined (Table 21, Entries 1 and 2). Unfortunately, the yield of **179a** decreased dramatically to 10% in the ChemScan II® reactor compared to 58% when a balloon of CO was used (Table 21, entries 1 *vs*. 2). ^{1}H NMR analysis of the crude reaction mixture from the ChemScan II® reactor revealed that the majority of the mass balance was protodecyclopropanted **178a** (for a discussion on degradation of substrates related to **178a**, see Section 3.1). It was postulated that the lack of any desired product may be due to the reversibility of rhodacyclopentanone formation (see mechanistic studies discussed in Section 2.6), combined with low concentration of CO in solution.[261] Consequently, the effect of CO pressure was evaluated. It was found that increasing the pressure of CO to 2 bar and then 3 bar gave an increase in yield of **179a** to 31% and 45% respectively (Table 21, entries 3 and 5). However, a further increase to 4 bar was not beneficial (Table 21, entries 7 and 8), presumably due to saturation of the Rh(I)-catalyst by CO. Decreasing the temperature of the reaction to 120 °C with 2 or 3 bar of CO was detrimental to the yield of **179a** (Table 21, entries 4 and 6). Further attempts to improve the yield by adjusting the concentration of CO at a pressure of 3 bar (0.3 M *vs.* 0.2 M *vs.* 0.5 M) provided no further improvement (Table 21, entries 5 *vs*. 9 *vs.* 10). Of note, minor quantities of unsaturated product **180a** were detected in all reactions (for discussion on formation of **180a** see Section 2.1). Ultimately, the best conditions for the ChemScanII® reactor are outlined in Table 21, entry 5, with an optimal CO pressure of 3 bar. By comparison to the original balloon conditions, the yield of cyclised product **179a** is slightly decreased (45% *vs.* 58%). However, more significantly, the reaction time was dramatically reduced (24 hours *vs.* 72 hours) and the loading of $P(4\text{-}FC_6H_4)_3$ was reduced (15.0 mol% *vs.* 22.5 mol%). *Additional details regarding reaction setup are provided in Experimental Section 7.5*. Whilst this result was pleasing, additional studies are still required to elucidate the exact effect of CO pressure on the formation of the active catalyst species and conversion of amide **178a** to cyclised product **179a**. Likewise, it may be interesting to investigate the suitability of this transformation to a flow reactor.[262]

5.2.4 Studies towards the post-cyclisation transformations

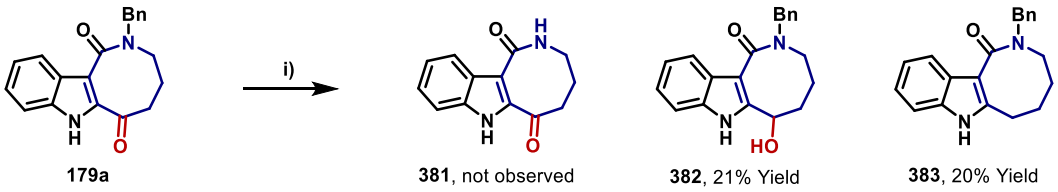
With a reliable supply chain of key intermediate **179a** established, investigations shifted towards completing the remaining transformations. As depicted in Scheme 111, it was hypothesised that lactam **179a** could be transformed into (*rac*)-conolidine through a series of carefully selected post-cyclisation manoeuvres. The four post-cyclisation transformations of **179a** included: 1) *N*-benzyl deprotection; 2) lactam reduction; 3) *N*-alkylation to install the *N*-vinyl halide unit; 4) construction of C15–C20 bond. At the outset, it was unclear what the exact order of these post-cyclisation transformations should be. Nonetheless, given the ease of substrate synthesis and the fact that a robust carbonylation protocol was already in place, we remained optimistic. A full description of these studies is outlined in the following sections.



Scheme 111: Post-cyclisation transformations of lactam **179a**.

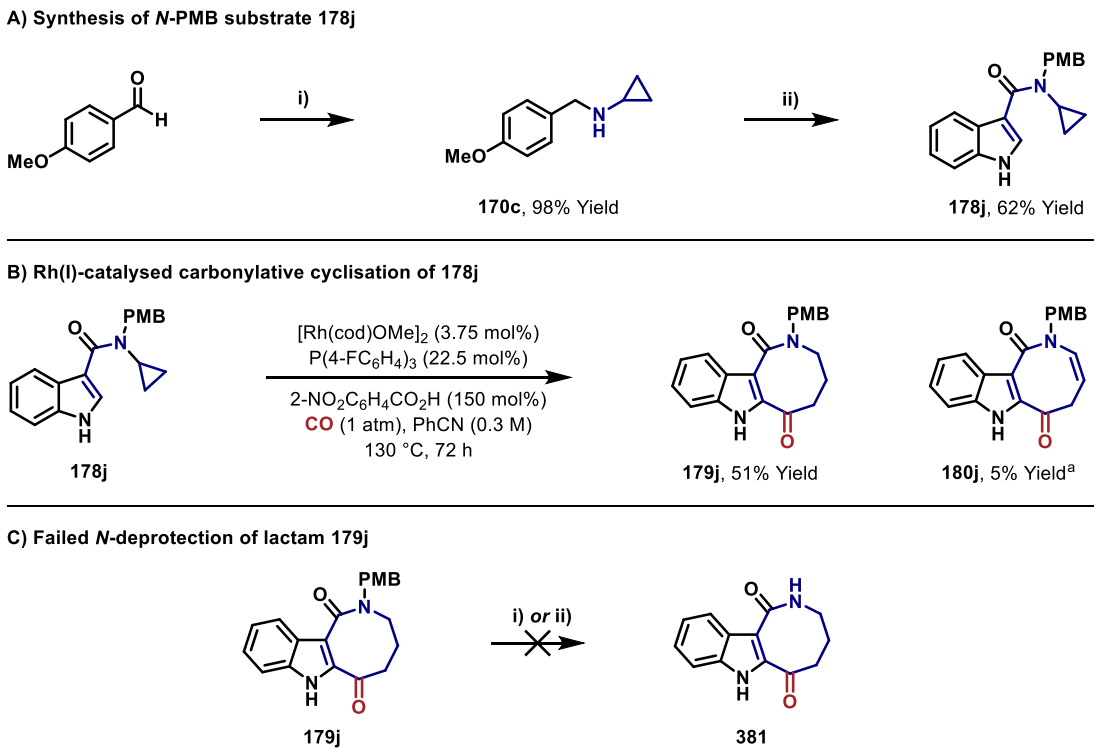
5.2.4.1 *N*-benzyl deprotection of a lactam

The first post-cyclisation transformation to be attempted was the removal of the *N*-benzyl protecting group from lactam **179a**. However, we were cautious about this synthetic manoeuvre as a potential drawback of using *N*-benzylamide protecting groups is that they can be challenging to remove, often requiring harsh conditions that are incompatible with other functional groups present in the molecule.[263] Indeed, attempts to remove the *N*-benzyl group from **179a** under hydrogenative conditions failed to provide the corresponding lactam **381**. Instead, reduction of the ketone carbonyl occurred, resulting in the formation of alcohol **382** and lactam **383** (Scheme 112).



Scheme 112: Failed *N*-benzyl deprotection of **179a**. *Reagents and conditions*: H-cube®, 0.05 M, 20% $Pd(OH)_2/C$, EtOH/EtOAc (2:1), 10 bar, 60 °C, 1 min min^{-1}.

Following this result, the *N*-benzyl group of **178a** was replaced with a more easily removable *N*-*p*-methoxybenzyl (PMB).[263] Amide **178j** was prepared in two steps and 61% yield, beginning with reductive amination of *p*-anisaldehyde with cyclopropylamine, followed by EDCI coupling of with 1*H*-indole-3-carboxylic acid (Scheme 113A). Under the established Rh(I)-catalysed carbonylation protocol developed in Section 2.4 ($[Rh(cod)OMe]_2$/ $P(4\text{-}FC_6H_4)_3$/$2\text{-}NO_2C_6H_4CO_2H$/PhCN/130 °C), **178j** readily cyclised, forming **179j** in 51% yield and with good selectivity over alkene **180j** (Scheme 113B, **179j**:**180j** = 10:1). With **179j** in hand, efforts to remove the *N*-PMB group under acidic conditions at elevated temperatures[264] or *via* oxidative conditions using ceric ammonium nitrate (CAN),[265] failed to provide the corresponding lactam **381**. Reaction monitoring by TLC showed no reactivity and consequently, no further investigations into the removal of the *N*-PMB group were pursued.



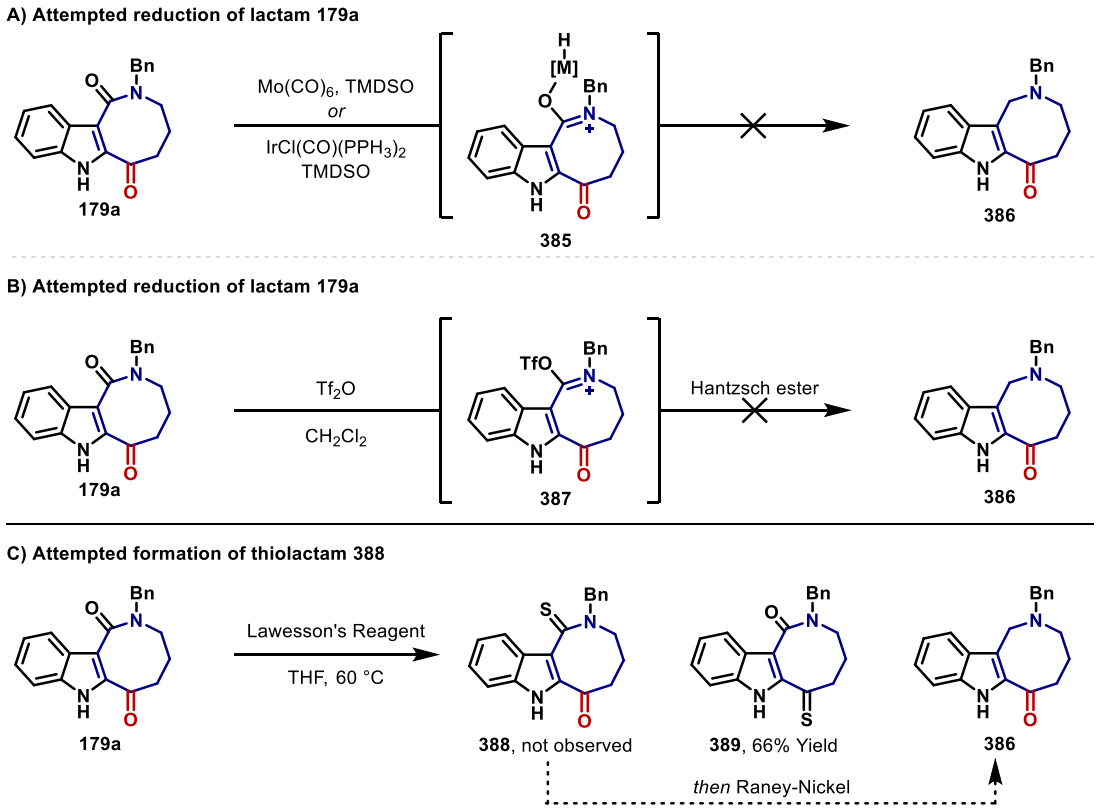
Scheme 113: A) *Reagents and Conditions*: i) cyclopropylamine, $NaHCO_3$, MeOH, reflux, 16 h *then* cool to 0 °C, $NaBH_4$, 16 h, 98%; ii) 1*H*-indole-3-carboxylic acid, EDCI, DMAP, CH_2Cl_2, r.t., 12 hours, 62%. C) *Failed conditions* i) TFA, CH_3Cl, 80 °C; ii) CAN, CH_3CN/H_2O (5:1), r.t. to 50 °C.

With the *N*-protecting groups of lactams **178a** and **179j** proving difficult to remove, it was decided to delay the *N*-deprotection step until later in the synthetic sequence. It was envisaged that either an *N*-benzyl group or an *N*-PMB group could be more readily removed from a cyclic amine compared to a lactam (*i.e.* re-attempt after the reduction of lactam **179a**, see Scheme 111).

5.2.4.2 Lactam Reduction

Based on the unsatisfactory results discussed above, investigations turned towards reduction of lactam **179a**. It was hoped that reduction of lactam **179a** could occur in the presence of the ketone functional group in order to eliminate unnecessary redox fluctuations.[266] However, the chemoselective reduction or lactams (or amides) in the presence of other reducible groups is highly challenging. Whilst significant progress has been made in the field of chemoselective amide reduction,[267] only a limited number of systems have demonstrated chemoselective reduction of amides over ketones[268-271] and a few of these have been successfully executed in natural product synthesis.[272-275] Among these methodologies, protocols that employ Lewis-acidic transition-metal hydrides that can selectively coordinate to the Lewis-basic amide carbonyl have emerged as particularly powerful methods. Unfortunately, several attempts to effect chemoselective amide reduction using $Mo(CO)_6$/TMDSO[269] or Vaska's catalyst ($Ir(CO)Cl(PPh_3)_2$ with TMDSO[276] did not generate **386** (Scheme 114A). Additionally, treatment of **179a** with triflic anhydride followed by addition of Hantzsch ester[268] was also unsuccessful (Scheme

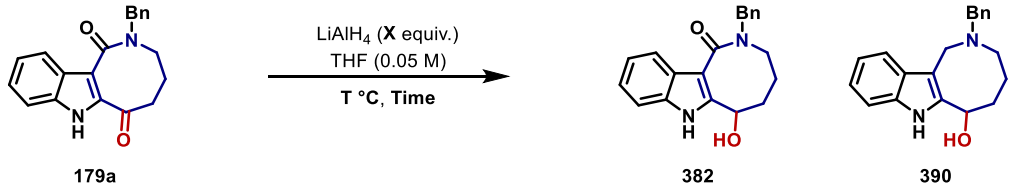
114B). Alternatively, it was anticipated that stepwise reduction of **179a** *via* thioamide formation (to **388**) and then treatment with Raney-Nickel may offer a potential solution to the problem.[273] However, it was found that treatment of **179a** with Lawesson's Reagent afforded thioketone **389** exclusively (Scheme 114C). Overall, the lack of desired activity exhibited by **179a** was believed to be a consequence of the conjugated indole unit, which made the activated intermediates (*i.e.* **385** and **387**) less electrophilic and the keto carbonyl more nucleophilic compared to the lactam carbonyl. Based on these results, it was evident that a stronger reducing agent would be required.



Scheme 114: Attempted chemoselective reduction of lactam **179a**.

Given the difficulty associated with chemoselective reduction of lactam **179a**, two solutions were proposed: (1) protection of the ketone functional group prior to reduction of the lactam carbonyl; or (2) global reduction of **179a** followed by re-oxidisation of the ensuing alcohol moiety. Both options meant the unavoidable inclusion of additional steps, but given the situation, it was deemed the most logical way to proceed. To initiate these studies, the global reduction of **179a** using $LiAlH_4$ was first investigated and key results are given in Table 22. Initially literature conditions were evaluated,[277] which led to the rapid consumption of **179a** and clean conversion to partially reduced intermediate **382** in 75% yield. However, the lactam carbonyl remained firmly intact. (Table 22, entry 1). Increasing the number of equivalents of $LiAlH_4$ and prolonging the reaction time generated the desired product **390** in 10% and 43% yield respectively (Table 22, entries 2 and 3), with the remaining mass balance consisting largely of partially reduced intermediate **382**. From these results, it was clear that the reduction of the

lactam moiety was incredibly sluggish and even more forcing conditions would be required. Ultimately, it was found that heating the reaction in a sealed tube at 80 °C with 2 equivalents of $LiAlH_4$ afforded product **390** in 87% yield (Table 22, entry 4). Finally, increasing the number of equivalents of $LiAlH_4$ from 2 to 3 gave a further increase in yield from 87% to 93% (Table 22, entry 5) From a safety perspective, sufficient material could be prepared by performing multiple reactions in parallel on 0.356 mmol scale in a sealed tube with a blast shield.

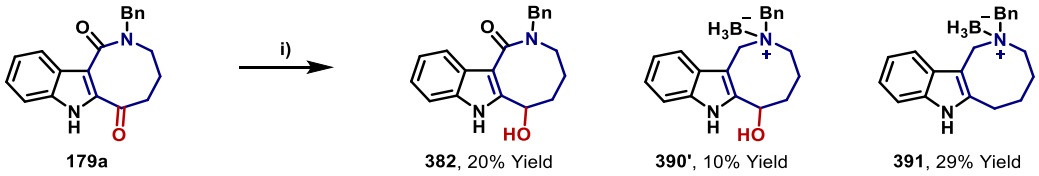


179a 382 390

Entry	X	T °C	Time	Yield 382[a]	Yield 390[a]
1[b]	1.0	0 °C to reflux	18 h	75%	-
2[b]	2.0	0 °C to reflux	72 h	10%	55%
3	3.0	0 °C to reflux	48 h	43%	35%
4[c]	2.0	0 °C to 80 °C	24 h	-	87%
5[c]	**3.0**	**0 °C to 80 °C**	**24 h**	**-**	**93%**

Table 22: Optimisation of the reduction of lactam **179a**. [a] Yields of isolated products are given unless stated otherwise. [b] The reaction molarity was 0.10 M. [c] Sealed tube was used with a safety shield.

In parallel studies, BH_3·THF was examined as an alternative reducing agent. Treatment of amide **179a** with 2 equivalents of BH_3·THF at reflux successfully reduced the lactam with concomitant borylation of the tertiary amine to give amine·BH_3 adduct **390'** in 10% yield (Scheme 115). However, partially reduced intermediate **382** and the over reduced amine·BH_3 adduct **391** were also isolated in 20% and 29% yield respectively. Although unintentional, the introduction of the amine-boron group proved beneficial as it masked the tertiary amine and facilitated purification; however, as the results outlined in Table 22 with $LiAlH_4$ proved far superior, no further investigations into borane reduction of **179a** were conducted.

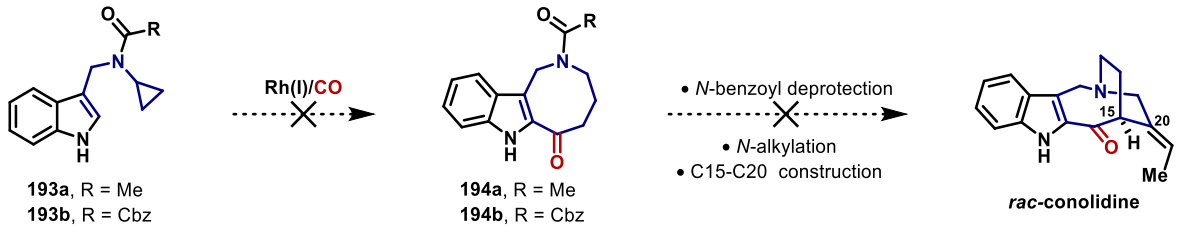


179a **382**, 20% Yield **390'**, 10% Yield **391**, 29% Yield

Scheme 115: *Reagents and conditions*: BH_3·THF (2.0 equiv.), THF, 0 °C to reflux, 48 h.

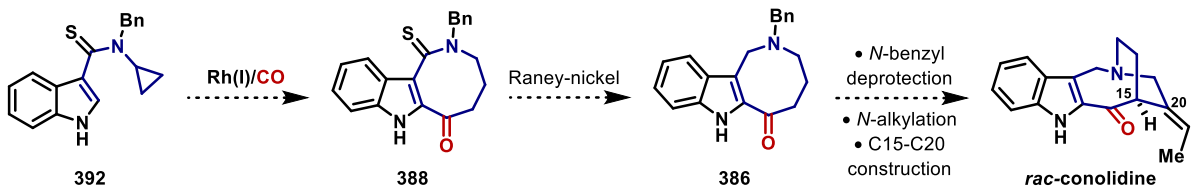
The studies into the reduction of lactam **179a** marked the first major crossroad in the synthesis of (*rac*)-conolidine, from which alternative scenarios could be envisioned. Therefore, before continuing with the synthesis, several aspects of the chosen reaction path and the thought process behind it deserve

additional comment. Firstly, an endocyclic amide directing group was essential for the Rh(I)-catalysed carbonylative cyclisation to proceed (see Chapter 2 and Section 2.6) but after this key step, its presence was redundant and a hinderance with respect to step count. As the Rh(I)-catalysed carbonylation was pivotal in the synthetic route, it was decided that the inclusion of an *endo* directing group was non-negotiable. Consistent with this notion, re-design of the carbonylative substrate **178a** to include an *exo* directing group (e.g. *N*-acetate **193a** or *N*-Cbz **193b**) was ruled out (Scheme 116). Despite the fact that successful formation of **194a** or **194b** would side-step the need for lactam reduction, there was no precedence for either **193a** or **193b** succeeding in the Rh(I)-catalysed carbonylation step. As demonstrated in Section 2.6, exposure of *N*-acetate **193a** to carbonylative conditions led only to decomposition pathways (see Scheme 54). Consequently, no studies were initiated into investigating the conversion of **193a/b** to **194a/b** and efforts focused solely on parent indole **178a** with the prerequisite *endo* directing group.



Scheme 116: Unsuitable substrates for construction of the eight-membered ring.

The downside of pursuing studies with amide **178a** was that subsequent reduction of lactam **179a** resulted in concomitant reduction of the keto carbonyl group. In contrast to lactams, thiolactams can be readily reduced; therefore, a potential solution to eliminating unnecessary redox steps involves switching the endocyclic amide directing group of **178a** for an endocyclic thioamide directing group. In unpublished work in the Bower group, G.-W. Wang has shown that thioureas are competent directing groups for the formation of 7-membered rings by carbonylative ring expansion of aminocyclopropanes.[278] Therefore, provided that thioamide **392** is a suitable candidate in the Rh(I)-catalysed carbonylation reaction, reduction of **388** with Raney-nickel[279] would avoid oxidation and re-oxidation of the keto carbonyl group (Scheme 117).



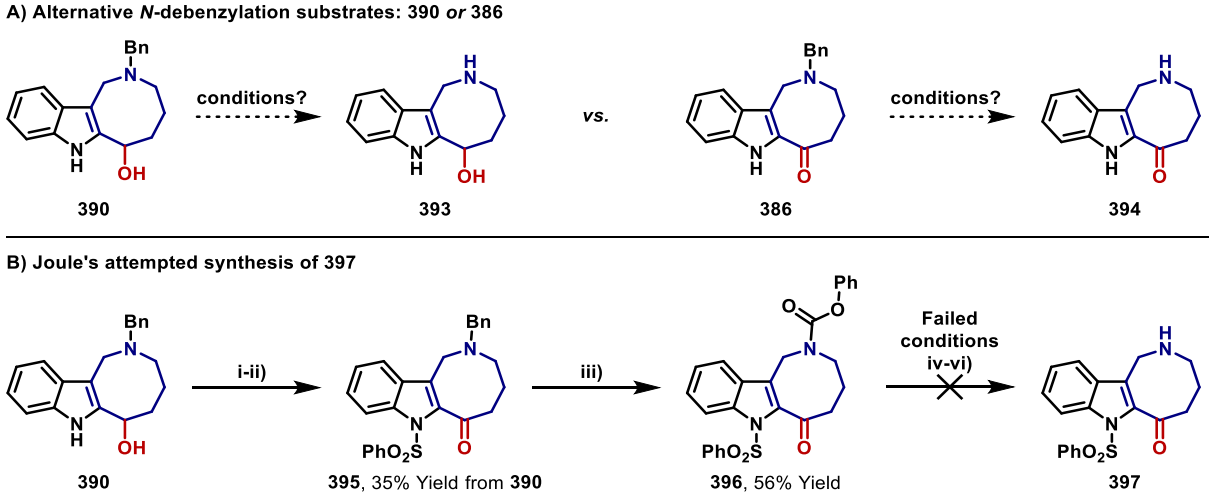
Scheme 117: Proposed use of thioamide **392**.

Furthermore, as stated previously, the avoidance of chemo-unselective reactions would allow for a reduction in the number of unnecessary redox steps and should be re-examined in future studies.

One strategy to overcome this shortcoming involves transiently protecting the more reactive carbonyl group of lactam **179a** and regenerating it after reduction of the less reactive lactam group. Common protocols that protect ketones *in situ* include nucleophilic addition of metal amides,[280] or phosphines[281] or masking the ketone as an enolate[282] prior to the addition of the reducing agent $LiAlH_4$ or BH_3·THF. Given the knowledge available at the time of these investigations, the decision was made to persevere and persist with the global reduction of **179a**. It was therefore accepted that adopting this strategy would inevitably lead to a longer route; however, this negative was outweighed by the anticipation that amine **390** could ultimately be transformed into conolidine.

5.2.4.3 *N*-Benzyl deprotection of an amine

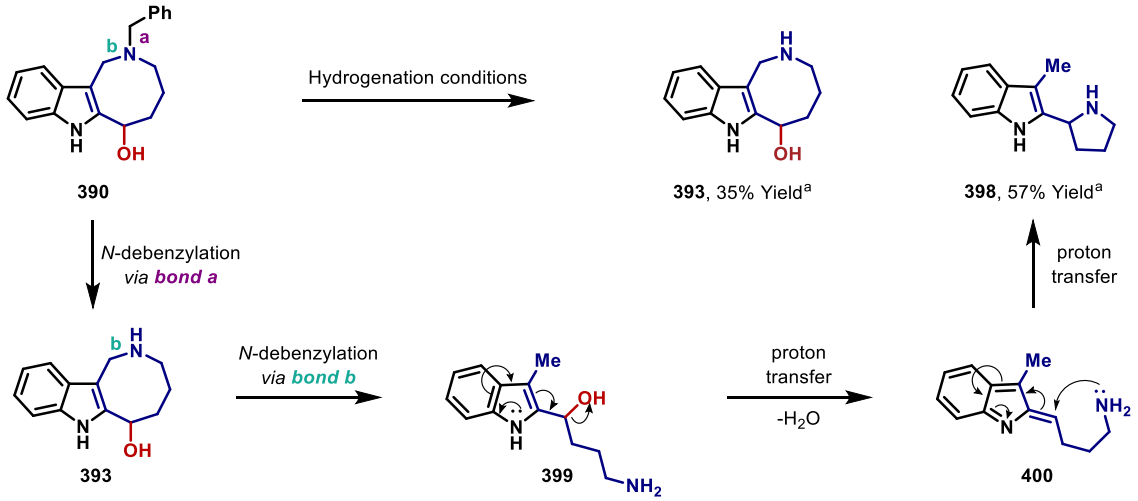
The next hurdle in the synthesis of (*rac*)-conolidine entailed the removal of the amine *N*-benzyl protecting group. For this transformation, it was not clear if *N*-debenzylation should be attempted directly from amine **390** or if oxidation of **390** to keto **386** should be conducted first (Scheme 118A). Nonetheless, we remained cautious about the suitability of substrates **390** and **386** as they both contain a potentially labile gramine fragment that could result in unravelling of the 8-membered ring. Additionally, we were hesitant to oxidise alcohol **390** prior to *N*-debenzylation, as studies by Joule reported that the product of straight forward *N*-benzyl removal (*i.e.* azocane **394**) could not be obtained.[283] Additional investigations by Joule revealed that the *N*-benzyl group of keto **395** could be removed, but only at the expense of replacing it with a phenyl carbamate, which was equally as stubborn to remove (Scheme 118B).[283]



Scheme 118: B) *Reagents and Conditions*: i) MnO_2, $CHCl_3$, r.t., 48 h, 53%; ii) benzenesulfonyl chloride, aq. NaOH, benzene, r.t., 1 h, 82%; iii) phenyl chloroformate, $KHCO_3$, $CHCl_3$, reflux, 8 h, 56%. *Failed conditions*: iv) aq. NaOH, reflux; v) NaH, THF, r.t.; vi) CH_3Li·LiBr complex in ether, THF 0 °C to r.t..

To gauge if substrate **390** was amenable to *N*-debenzylation, hydrogenative conditions were trialled in flow with 5% Pd/C at 1 bar and 80 °C.[284] Surprisingly, ring contracted pyrrolidine **398** was

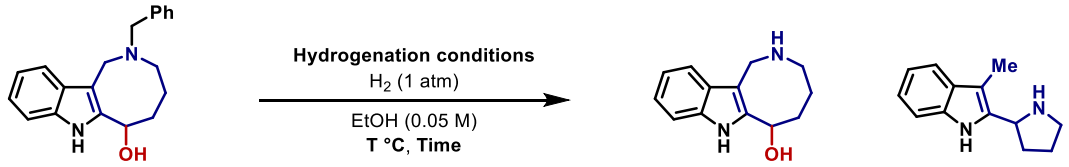
observed as the major product in 57% yield, along with the desired secondary amine **393** in 35% yield (Scheme 119), suggesting that this transformation was not as simple as originally thought. This result raised two critical issues: (i) which benzylic position of **390** undergoes debenzylation first; and (ii) is the desired product **393** only unstable under hydrogenative conditions *or* is it predisposed to undergo fragmentation. Understanding these concepts was of upmost importance if the synthetic route was to succeed.



Scheme 119: *N*-debenzylation of substrate **390** under hydrogenation conditions. *Reagents and conditions*: H-cube®, 0.05 M, 5% Pd/C, EtOH, 1 bar, 80 °C, 1 min min^{-1}. [a] The yield was determined by ^{1}H NMR analysis using 1,4-dinitrobenzne as an internal standard.

A plausible mechanism for the formation of pyrrolidine side product **398** is outlined in Scheme 119. In agreement with literature, it is proposed that *N*-debenzylation occurs first *via bond* ***a*** to give the desired product **393**.[284,285] A second debenzylation *via bond* ***b*** breaks the 8-membered ring, generating linear analogue **399**. At this stage, the nucleophilic indole core triggers a cascade reaction, eliminating a molecule of water to give **400**. Nucleophilic attack by the pendant NH_2 moiety on the resulting C-sp^2 centre, followed by restoration of the aromatic indole unit affords **398**. Cationic cascades involving the indole unit of structurally similar analogues have been reported in the literature.[286,287] The facile fragmentation of **393** under hydrogenation conditions undoubtedly reflects the activation of *bond* ***b*** by the strained 8-membered ring, which is enhanced further by the nucleophilic indole core. Indeed, it has been observed previously that *N*-protecting group removal from tertiary amines structurally related to **390**/**386** can be challenging as such substrates are prone to fragmentation by C–N bond cleavage (*i.e. via* cleavage of bond **b**). In some cases, this can be controlled by the introduction of an electron withdrawing group (*e.g.* Boc, benzoyl or tosyl group) on the indole nitrogen atom.[288] However, with regards to the synthesis of conolidine, the introduction and subsequent removal of a nitrogen indole protecting group was undesirable.[289] Therefore, in line with these thoughts, efforts focused on

preventing the unwanted double debenzylation of **390**. Subsequent optimisation studies were performed in batch with a balloon of H_2 and key results are presented in Table 23.



390 **393** **398**

Entry	Pd Source	mol% Pd	T °C	Time	Remaining 390[a]	Yield 393[a]	Yield 398[a]
1	10 wt.% Pd/C	5 mol%	r.t.	23 h	100%	-	-
2	10 wt.% Pd/C	100 mol%	r.t.	23 h	-	43%	49%[b]
3	10 wt.% Pd/C	5 mol%	40 °C	23 h	80%	7%[b]	10%[b]
4	10 wt.% Pd/C	50 mol%	45 °C	23 h	-	-	92%
5	20 wt.% $Pd(OH)_2$	50 mol%	r.t.	18 h	-	65%	25%
6	20 wt.% $Pd(OH)_2$	20 mol%	r.t.	18 h	15%	61%	yes by TLC
7	20 wt.% $Pd(OH)_2$	20 mol%	r.t.	13 h	37%	57%	<5%[b]
8	20 wt.% $Pd(OH)_2$	10 mol%	r.t.	23 h	15%	45%	30%

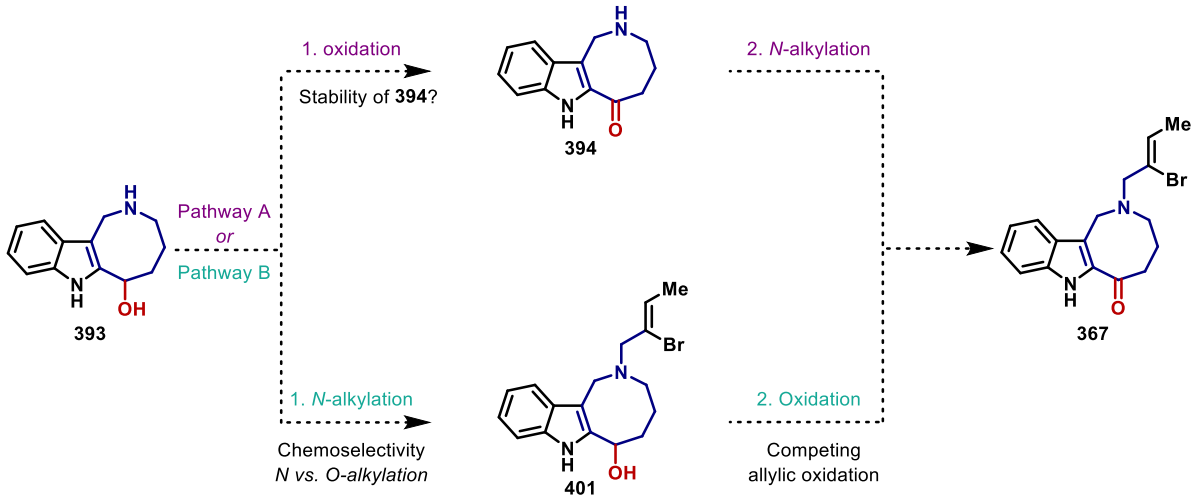
Table 23: *N*-debenzylation of substrate **390** under hydrogenation condition. [a] Yields of isolated products unless stated otherwise. [b] The yield was determined by ^{1}H NMR analysis using 1,4-dinitrobenzne as an internal standard.

The use of 5 mol% Pd/C (10 wt. %) in ethanol with an atmospheric pressure of H_2 did not promote *N*-benzylation deprotection at room temperature (Table 23, entry 1). It was found that adjusting the molar ratio of **390**:Pd/C (1:0.05 to 1:1) resulted in complete consumption of starting material **390**, affording desired product **393** in 43% and side-product **398** in 49% yield (Table 23, entry 2). Based on this insight, the quantities of Pd/C were systematically examined (100−50 mol%, results not provided in Table 23) but over reduced side-product **398** was detected in all reactions. Performing the reaction at 40 °C with 5 mol% Pd/C led only to a 7% *in situ* yield of **393**, with the majority of the mass balance being starting material **390** (Table 23, entry 3). Attempts to accelerate the process by increasing the loading of Pd/C to 50 mol% and heating the reaction at 45 °C led solely to side-product **398** in 92% yield (Table 23, entry 4). Performing the reaction with 50 mol% of $Pd(OH)_2$ (20 wt. %) (Pearlman's catalyst[290]) at room temperature gave the desired secondary amine **393** in 65% yield, with only 25% of the side-product **398** (Table 23, entry 5). In an effort to minimise the amount of catalyst available to effect debenzylation, the loading of $Pd(OH)_2$ was reduced to 20 mol% and this led to a further reduction in **398** but importantly maintained good yields of **393** (61% yield, Table 23, entry 6). Despite best efforts to curtail the formation of **398** (by careful control of time and reaction monitoring by TLC) its formation could not be fully eliminated; however, shortening the reaction time to 13 hours gave the best result in

terms of isolated yield of **393** and recovered starting material **390** (57% **393**, 37% **390**, Table 23, entry 7). Indeed, using these conditions, multiple reactions were set up in parallel, allowing enough material to be prepared. Moreover, appreciable amounts of **390** were recovered and re-subjected to hydrogenolysis. This result marked a significant milestone towards completing the total synthesis of (*rac*)-conolidine. It should be noted that all experiments were conducted with high dilution (0.05 M) and typically on 0.100–0.188 mmol scale. Consequently, future studies will focus on the scalability of this process with respect to $Pd(OH)_2$ loading and reaction molarity.

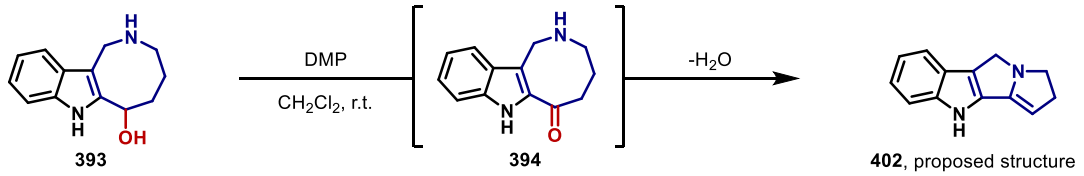
5.2.4.4 Benzyl oxidation and *N*-alkylation

With appreciable amounts of amine **393** in hand, the next objective of the project was to prepare cyclisation precursor **367**. It was envisaged that **367** could be formed by a straightforward sequence of oxidation and *N*-alkylation. However, the exact order of these two transformations remained unclear, with potential pitfalls arising from either option (Scheme 120).



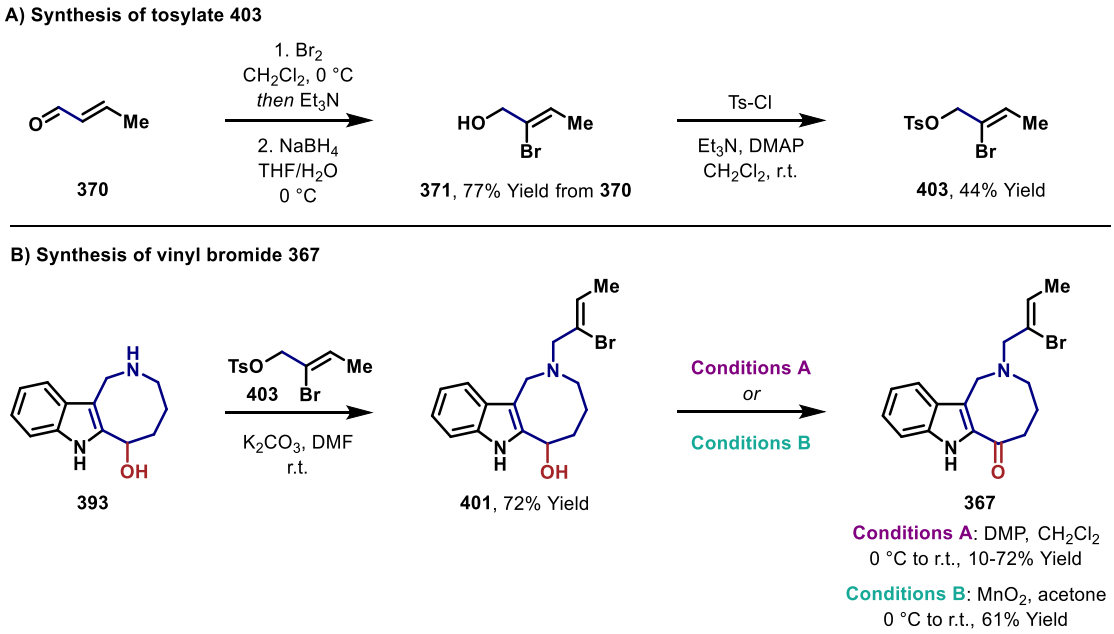
Scheme 120: Alternative synthetic sequences to access cyclisation precursor **367**.

In order to quickly ascertain the feasibility of pathway A, oxidation of alcohol **393** was attempted using Dess-martin periodinane (Scheme 121).[291] Reaction monitoring by LCMS indicated formation of keto **394**, but attempts to isolate the desired product were unsuccessful (presumably by decomposition on basic HPLC column) and therefore structure **394** was proposed tentatively. It was postulated that putatively formed **394** was prone to spontaneous transannular condensation of the secondary amine onto the newly formed ketone moiety, which after tautomerization led to cyclic amine **402**. Previously Bennasar has reported that compounds akin to **394** are prone to undesired fragmentation pathways.[250] The structure of side product **402** was not confirmed but tentatively assigned based on comparison with data available in the literature.[283] No attempt was made to investigate this reaction further or explore alternative oxidising reagents.



Scheme 121: Attempted oxidation of alcohol **393**.

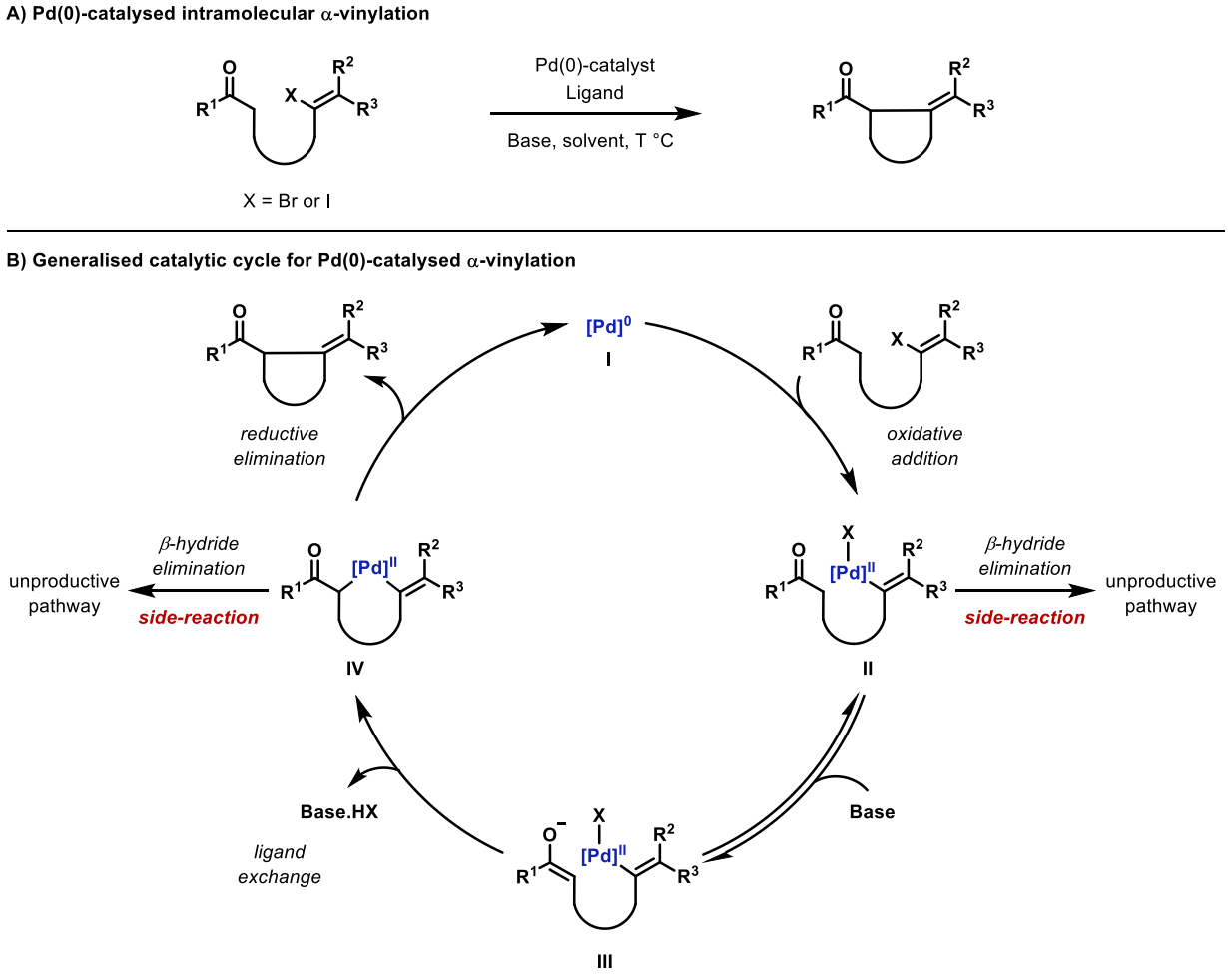
Since the stability of keto **394** proved problematic, subsequent studies focused on a reversal of step order, in which *N*-alkylation preceded oxidation of the alcohol (Pathway B, Scheme 120). Gratifyingly, this decision proved fruitful. Tosylate **403** was chosen as the alkylating reagent and following a literature procedure, was readily prepared in three steps from *trans*-crotonaldehyde **370** (Scheme 122A).[251] With potassium carbonate as the base, *N*-alkylation of **393** with tosylate **403** (1.0 equiv.) was readily carried out in DMF at room temperature to provide vinyl bromide **401** in 72% yield (Scheme 122B). Following the appendage of the *N*-vinyl halide segment, attention turned to oxidation of alcohol **401**. When Dess-Martin periodinane was used as the oxidant, the reaction exhibited poor reproducibility, with yields ranging from 10−72%; attempts to identify the cause of this fluctuation were unsuccessful (fresh Dess-Martin periodinane reagent, inert conditions, lower temperature). Alternatively, when MnO_2 was used in acetone, the reaction exhibited a cleaner reaction profile and cyclisation precursor **367** could be obtained in 61% yield.[292] Using this sequence of events, both the *N*-alkylation and benzyl oxidation could be performed reliably to provide adequate quantities of **367**. With vinyl bromide **367** in hand, the stage was set to complete the synthesis of (*rac*)-conolidine.



Scheme 122: Synthesis of vinyl bromide **367**.

5.2.4.5 Palladium catalysed α-vinylation

The final challenge in the total synthesis of conolidine involved construction of the hallmark azabicyclo[4.2.2]decane core. At the outset of the project, it was envisioned that stereospecific unification between the geometrically-defined vinyl bromide unit of **367** with its ketone enolate would be achieved by Pd(0)-catalysis (see Scheme 109). The direct alkenylation of carbanion nucleophiles with vinyl halides is one of the most efficient and economic methods for installing β-γ unsaturated units, and palladium is more often than not the catalyst of choice for such processes.[293] However, compared to related arylation reactions with aryl halides,[294-297] α-alkenylation reactions remain in relatively early stages of development. A generalised catalytic cycle for Pd(0)-catalysed intramolecular couplings of ketone enolates with tethered alkenyl halides is provided in Scheme 123.

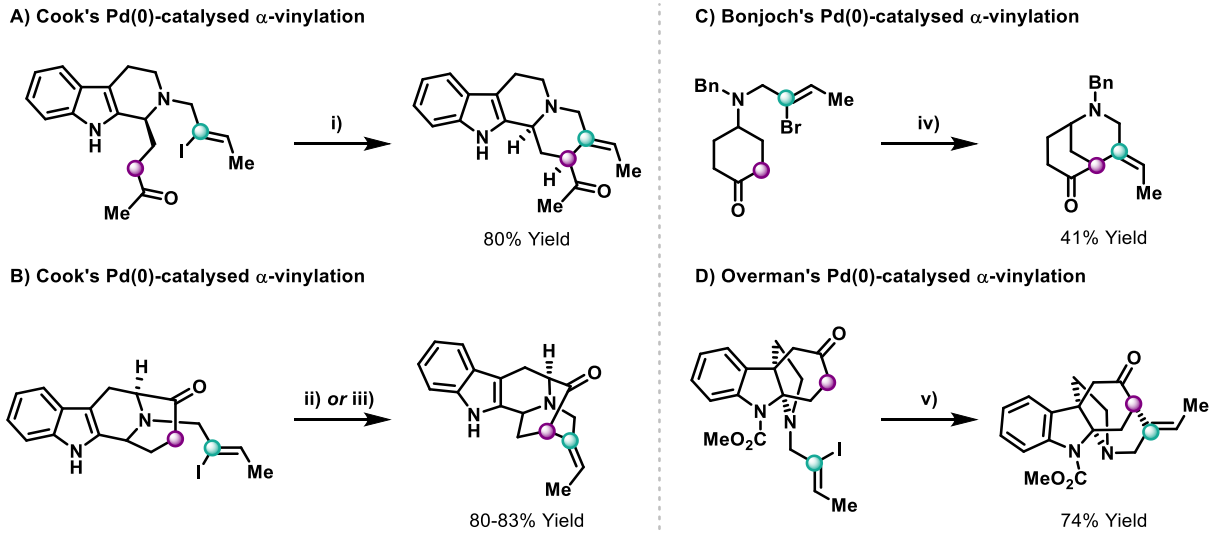


Scheme 123: Generalised catalytic cycle for Pd(0)-catalysed intramolecular coupling of ketone enolate and vinyl halide.

As depicted in Scheme 123, oxidative addition of an alkenyl halide with a suitable Pd(0)-catalyst forms intermediate **II**. Base induced ligand exchange of the coordinated halide by the ketone enolate nucleophile *via* **III** generates Pd(II)-intermediate **IV**. Reductive elimination from the

Pd(II)-enolate complex **IV** provides α-vinyl ketone product and regenerates the Pd(0)-catalyst. The exact structure of the Pd(II)-enolate intermediate **IV** remains unclear (O-bound *or* C-bound to Pd(II) -centre) and may vary from substrate to substrate.[298] While α-alkenylation and α-arylation of enolates are considered to be similar reactions, the later presents additional challenges. For example, Pd(II) intermediates (*i.e.* **II**, **III** and **IV**), are prone to side reactions, such as β-hydride elimination or protodehalogenation, which can outcompete the productive pathway of ligand exchange and reductive elimination. Additionally, under basic conditions, issues arise with respect to the stereoidentity of secondary and tertiary α-alkenylated products, due to *cis*/*trans* isomerisation or isomerisation to an α,β-unsaturated compound.[299,300] What is more, alkali metal enolates are typically generated at low temperatures, but cross-coupling is usually conducted at elevated temperatures. Therefore, there is a fine balance to be struck between stability (to avoid decomposition pathways and undesired β-hydride elimination) and reactivity (to promote efficient ligand exchange and reductive elimination).

Before revealing the final investigations of this target, a brief survey of selected chemical literature relating to intramolecular Pd(0)-catalysed α-vinylation reactions will be given. The first intramolecular Pd(0)-catalysed α-vinylation was reported by Piers and co-workers in the total synthesis of diterpenoid crinipellin B in 1990.[301] Since this seminal report, Pd(0)-catalysed intramolecular α-vinylation of keto enolates has proven to be an indispensable tool for the construction of bridged carbocyclic ring systems in natural product targets. Insightful studies by Cook,[302-304] Bonjoch[299] and Overman[305] have pioneered work in this field and four impressive examples from these laboratories are summarised in Scheme 124.

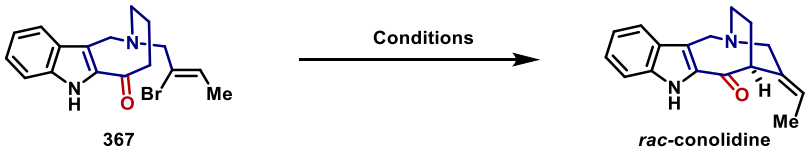


Scheme 124: Selected literature examples for Pd(0)-catalysed α-vinylation reactions of substrates structurally related to vinyl bromide **367**. A) *Reagents and conditions*: i) $Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), K_2CO_3 (4.0 equiv.), Bu_4NBr (1 equiv.), DMF/H_2O (9:1), 65 °C, 80%. B) *Reagents and conditions*: ii) Pd_2dba_3 (5 mol%), DPEPhos (7 mol%), NaO*t*-Bu (1.5 equiv.), THF, 80 °C, 80% *or* iii) $Pd(PPh_3)_4$ (10 mol%), PhOH (2.0 equiv.), KO*t*-Bu (1.5 equiv.), THF, 75 °C, 83%. C) *Reagents and conditions*: iv) $Pd(PPh_3)_4$ (20 mol%), KO*t*-Bu (1.5

equiv.), THF, reflux, 41%. D) *Reagents and conditions*: v) $PdCl_2(dppf)$ (10 mol%), K_2CO_3 (4.0 equiv.), MeOH, 70 °C, 74%.

Of note, the conditions identified by Cook and Overman are highly robust and have been utilised in the total synthesis of a wide range of natural product targets.[303-319] To the best of our knowledge, there are no reported α-vinylation reactions involving (aza)cyclooctane rings to produce bridged ring systems.[320] Additionally, a small number of enantioselective Pd(0)-catalysed enolate alkenylations have been reported through the use of chiral phosphine ligands.[321-323]

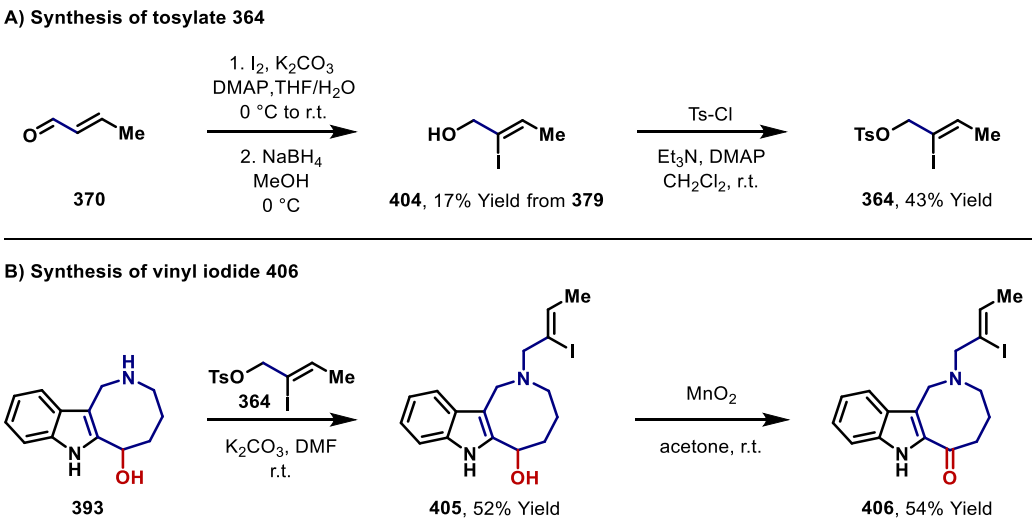
Following this survey, it was decided that the literature conditions presented in Scheme 124 would be examined first to install the final C–C bond of (*rac*)-conolidine. The results of these reactions are summarised in Table 24.



Entry	Conditions	Results/Observations
1	$PdCl_2(dppf)$ (10 mol%), K_2CO_3 (4.0 equiv.) MeOH, 70 °C	No starting material remaining. Complex mixture.
2	$Pd(OAc)_2$ (5 mol%),PPh_3 (20 mol%), K_2CO_3 (4.0 equiv.) Bu_4NBr (1 equiv.), DMF/H_2O (9:1), 65 °C	No starting material remaining. Complex mixture.
3	Pd_2dba_3 (5 mol%), DPEPhos (7 mol%), NaO*t*-Bu (1.5 equiv.) THF, 80 °C	No starting material remaining. Complex mixture.
4	$Pd(PPh_3)_4$ (10 mol%), PhOH (2.0 equiv), KO*t*-Bu (1.5 equiv.) THF, 75 °C	Degradation.

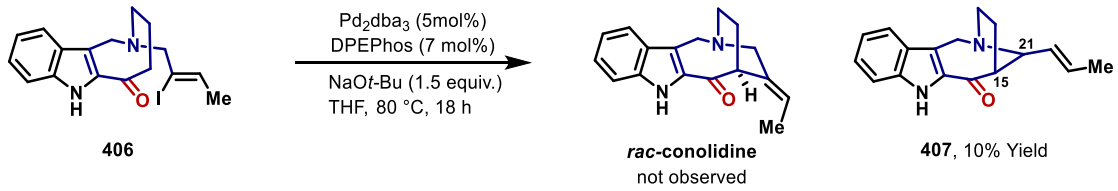
Table 24: Attempts to execute Pd(0)-catalysed intramolecular α-vinylation of **367**.

Disappointingly, all attempts to effect formation of (*rac*)-conolidine failed, and instead, nonspecific decomposition of **367** occured, with none of the desired product observed by ^{1}H NMR analysis. Thus, despite the excitement of having overcome a magnitude of synthetic challenges so far, it was evident that further modification of the synthetic plan would be required in order to achieve the definitive goal of the project. Undeterred by this initial disappointment, it was surmised that perhaps the low efficiency may be attributed to the low reactivity of alkenyl bromide **367**, given that alkenyl iodides are generally required in Pd(0)-mediated cyclisations within the context of total syntheses (for selected examples see Scheme 124). Accordingly, tosylate **364** possessing a vinyl iodide appendage was prepared following a three-step literature procedure (Scheme 125A).[251,324] *N*-Alkylation of secondary amine **393** with tosylate **364**, and subsequent MnO_2 mediated oxidation provided the requisite ketone vinyl iodide substrate **406** in 28% yield for the two steps (Scheme 125B).



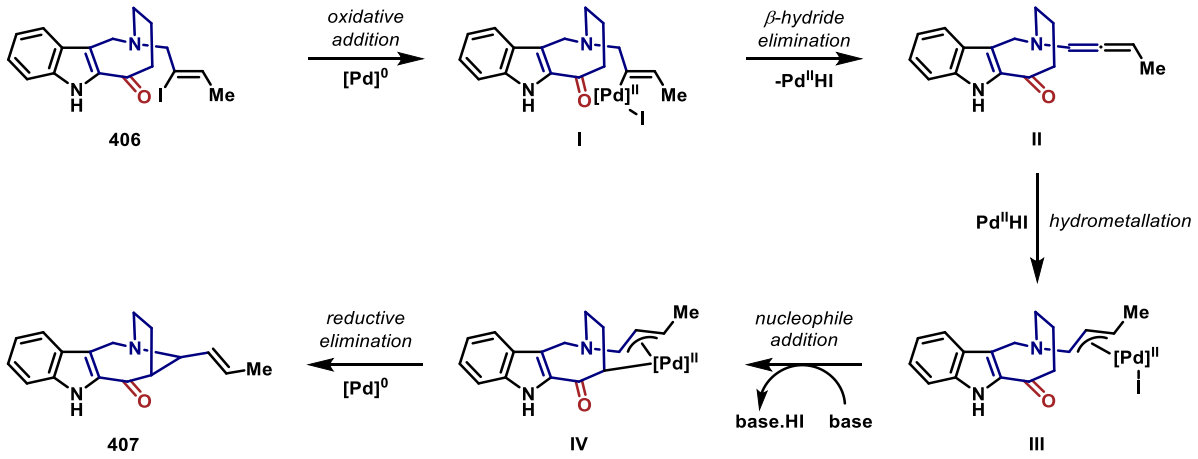
Scheme 125: Synthesis of tosylate **364** and vinyl iodide **406**.

With vinyl iodide **406** in hand, attention turned to the critical Pd(0)-catalysed intramolecular α-vinylation (Scheme 126). Exposure of a THF solution of **406** to Pd_2dba_3 (5 mol%), DPEPhos (7 mol%) and NaO*t*-Bu (1.5 equiv.) resulted in complete consumption of starting material after 18 hours at 80 °C. ^{1}H NMR and LCMS analysis of the crude reaction mixture indicated the formation of multiple products with the desired mass. Importantly, products of protodeiodination of **406** were not observed. Meticulous purification of the crude material by HPLC led to the isolation and characterisation of bicycle **407**, which contains an unusual azabicyclo[4.2.1]nonane core. The alkene geometry of **407** was confirmed to be *trans* by the diagnostic coupling constant of 13.5 Hz between the alkenyl protons. The relative stereochemistry of the C15 and C21 stereocenters was not determined.



Scheme 126: Pd-catalysed intramolecular α-vinylation of **406**. Compound **407** was isolated as its HCl salt.

On the basis of literature reports,[325-327] a plausible mechanism for the conversion of **406** to **407** is outlined in Scheme 127. First, oxidative addition of Pd(0) into the C–I bond of **406** generates species **I**. Subsequent β-hydride elimination generates allene **II** and a Pd(II)-hydride species. Insertion of allene **II** into Pd(II)-H forms Pd-π-allyl species **III**, which can be trapped by the keto enolate under basic conditions to give **IV**. Reductive elimination of **IV** delivers the observed product **407** and regenerates the Pd(0)-catalyst. An alternative reaction pathway involving E2 elimination of HI (*i.e.* generation of alkyne **411**, see Table 25), followed by alkyne/allene isomerisation and Pd-π-allyl formation cannot be ruled out.[328]



Scheme 127: Proposed mechanism for the formation of bicycle **407**.

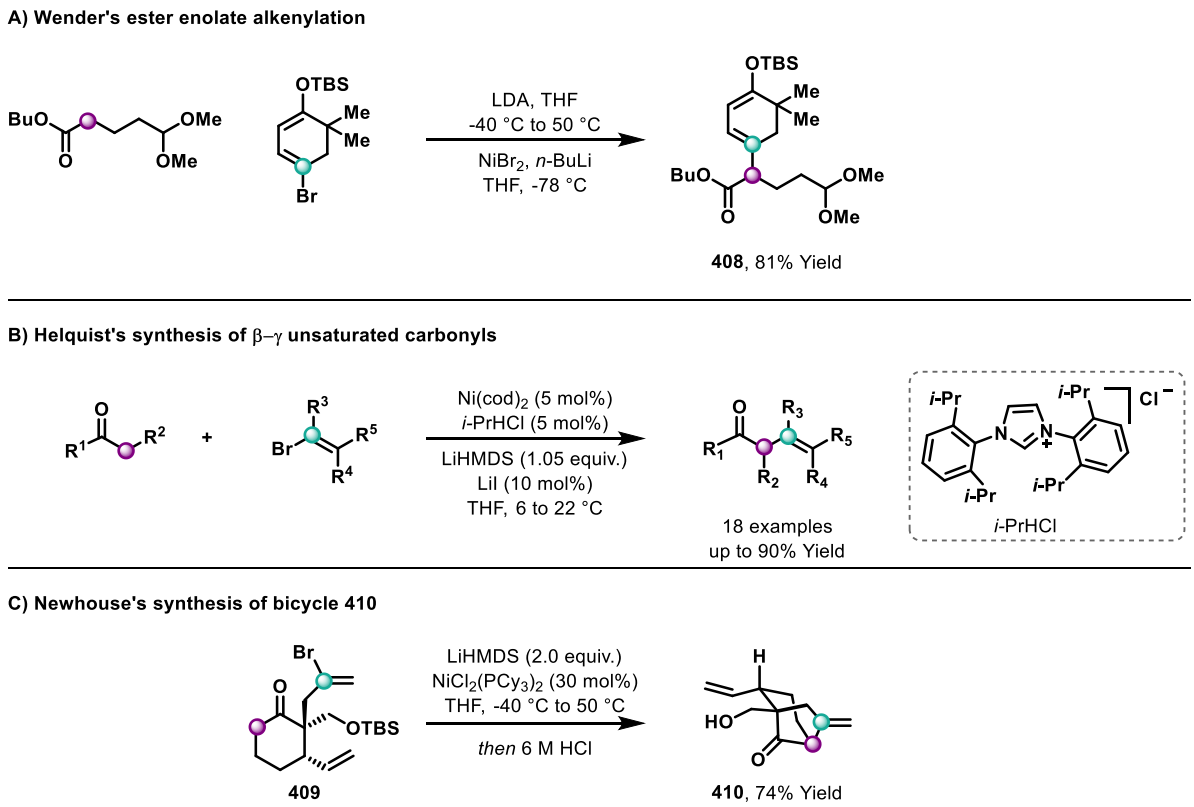
From this preliminary result, it was clear that deleterious β-hydride elimination pathways were inhibiting the desired transformation to form (*rac*)-conolidine. Palladium readily undergoes β-hydride elimination but it can be eliminated/suppressed through the inclusion of sterically demanding ligands, which either restrict β-hydride elimination and/or promote faster reductive elimination.[329] Consequently, a brief screen of bulky phosphine ligands (BINAP, Xanthphos, PCy_3) was undertaken using Pd_2dba_3 and NaO*t*-Bu in THF at 80 °C. However, efforts were quickly thwarted as each of these attempts resulted in highly complex reaction mixtures, with no formation of (*rac*)-conolidine detected by ^{1}H NMR analysis. With limited options remaining and an ever depleting supply of precursor **406**, it was hypothesised that alternative transition-metal catalysts may offer a potential solution to this final transformation. With this in mind, we turned to nickel, and thus, the fate of the synthesis relied upon identifying a suitable nickel-catalysed α-vinylation protocol.

5.2.4.6 Nickel catalysed α-vinylation and completion of the total synthesis of (rac)-conolidine

The field of nickel catalysis has expanded rapidly over the last twenty years and this is reflected by the highly diverse nickel-catalysed processes reported in the literature.[330] There are significant differences in reactivity between nickel and palladium, which play an important factor in catalyst selection. Firstly, nickel is more electropositive compared to palladium and therefore undergoes oxidative addition more readily.[331] This facile oxidative addition of nickel means that a broad range of adaptable electrophiles, that would be considerably less reactive under palladium catalysis, such as phenols, aromatic nitriles or aryl fluorides can be utilised. Conversely, reductive elimination from nickel centres is more difficult.[332] Additionally, β-hydride elimination tends to be slower with nickel, relative to palladium, due to a higher energy barrier to Ni–C bond rotation prior to β-elimination.[333] Consequently, the inherent reluctance of nickel to undergo β-hydride elimination can be advantageous in certain scenarios. Within the context of Ni(0)-catalysed Heck reactions, undesired β-hydride elimination can be avoided by tuning the coordination environment around nickel by strategically placing nitrogen atoms on the substrate.[334]

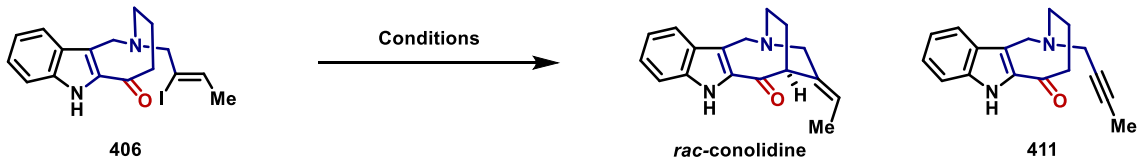
Empowered by the notion that such an interaction could be exploited between substrate **406** and a suitable nickel catalyst, we set out to investigate a nickel-mediated α-vinylation to construct the azabicycle[4.2.2]decane scaffold of (*rac*)-conolidine. Exciting precedent for this transformation will be discussed briefly in the following section.

In 1977 Rathke reported the first alkenylation of an ester enolate using a "ligand free" nickel species in stoichiometric quantities.[335] Capitalising upon this discovery, Wender applied the procedure to the total synthesis of quadrone in 1985, through the synthesis of intermediate **408** (Scheme 128A).[336] However, despite these early advances, there is a scarcity of reported nickel-catalysed α-vinylation reactions of keto enolates in the literature.[293] In contrast, nickel catalysed arylation of keto enolates reactions are marginally more common.[296,337,338] In 2015, Helquist reported a nickel catalysed intermolecular coupling of an aromatic or aliphatic ketone lithium enolate with a variety of alkenyl halides under relatively mild conditions (Scheme 128B).[339] Their protocol allowed for retention of β-γ unsaturated products, without migration or *cis*/*trans* isomerisation. Another advantage of this method includes short reaction times at low temperatures and only 1.05 equivalent of base was needed to deprotonate the ketone and NHC precursor. By comparison, Pd(0)-catalysed α-vinylations typically employ 1.5–4.0 equivalents of base due to the increased acidity of α-hydrogens in the product.[340] More recently, Newhouse took advantage of a Ni(0)-catalysed α-vinylation reaction to construct the bicyclo[3.2.1]octane fragment of Pincipinol D.[341] The authors reported that Ni-catalysed vinylation of 1,1-disubstitued vinyl bromide **409**, and subsequent hydrolysis formed bicycle **410** in an impressive 74% yield (Scheme 128C).[341] Air-stable nickel pre-catalyst $Ni(cod)_2(PCy_3)_2$ was utilised in this reaction, which obviates the need for air sensitive $Ni(cod)_2$, and results in a simpler reaction set-up.



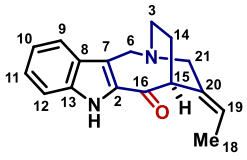
Scheme 128: Reported literature examples of Ni-catalysed α-vinylation.

On the basis of these literature examples from Helqvist and Newhouse, Ni-catalysis was employed for the final C–C bond forming reaction in the total synthesis of (*rac*)-conolidine. The results of this critical transformation are summarised in Table 25. Toward this end, cyclisation precursor **406** was exposed to 2.0 equiv. of LiHMDS and 30 mol% $Ni(cod)_2(PCy_3)_2$ in THF at 0 °C and then heated at 50 °C. Formation of (*rac*)-conolidine was observed through diligent examination of the ^{1}H NMR spectrum of the crude reaction mixture, albeit in minute quantities (<5%). The major identifiable side product was alkyne **411**, which most likely occurs through an E2 elimination pathway.[301] More significantly, no products arising from either protodeiodination or undesired β-hydride elimination pathways (*i.e.* formation of bicycle **407**) were observed by ^{1}H NMR analysis. Chromatographic purification of the reaction mixture afforded a 26% isolated yield of **411**. Unfortunately, efforts to isolate an analytical sample of (*rac*)-conolidine failed, most likely as a consequence of the low conversion coupled with the scale of the reaction (*the theoretical maximum yield of (rac)-conolidine was 13.5 mg*). Strong evidence for the formation of (*rac*)-conolidine comes from comparison of ^{1}H and ^{13}C NMR data of the crude reaction mixture with data reported in the literature.[221,237,247] These assignments are further corroborated by 2D COSY and HSQC data. The assignment and comparison of diagnostic ^{1}H and ^{13}C signals are provided in Table 26 and Table 27.



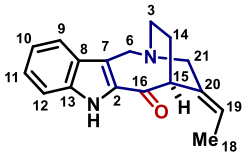
Entry	Conditions	Results/Observations
1	$NiCl_2(PCy_3)_2$ (30 mol%), LiHMDS (2.0 equiv.) THF, 0 °C to 50 °C	No starting material remaining. ^1H, ^{13}C, COSY and HSQC spectra of crude reaction mixture support formation of (*rac*)-conolidine. **411** isolated in 26% Yield.[a]
2	$Ni(cod)_2$ (10 mol%), *i*-PrHCl (10 mol%) LiHMDS (1.05 equiv.) THF, 0 °C to 40 °C	No starting material remaining. Complex mixture.

Table 25: Ni-catalysed α-vinylation of vinyl iodide **406**. [a] An *in situ* yield of (*rac*)-conolidine was not obtained.



Proton Number	Kam and coworkers[220] Natural (+)-conolidine ^1H NMR, 400 MHz, $CDCl_3$ ^1H [δ (ppm), multi., *J* (Hz)]	This report Synthetic (*rac*)-conolidine ^1H NMR, 500 MHz, $CDCl_3$ ^1H [δ (ppm), multi., *J* (Hz)]
3	3.09 (dddd, *J* = 14.0, 10.0. 8.0. 1.0 Hz)	
3	3.40 (ddd, *J* = 14.0, 8.5, 3.0 Hz)	3.41 (m)
6	4.29 (d, *J* = 18.5 Hz)	4.27 (d, *J* = 18.5 Hz)
6	4.77 (d, *J* = 18.5 Hz)	4.78 (d, *J* = 18.5 Hz),
9	7.57 (br. dd, *J* - 8.0, 1.0 Hz)	7.56 (d, *J* = 8.0 Hz)
10	7.11 (ddd, *J* = 8.0, 6.0, 2.0 Hz)	
11	7.33 (ddd, *J* = 8.5, 6.0, 1.0 Hz)	
12	7.36 (ddd, *J* = 8.5, 2.0, 0.5 Hz)	
14	2.05 (ddd, *J* = 15.0, 8.0, 3.0 Hz)	
14	2.14 (dddd, *J* = 15.0, 10.0, 8.5, 6.5 Hz)	
15	3.98 (br. d, *J* = 6.5 Hz)	3.97 (d, *J* = 7.0 Hz)
18	1.51 (ddt, *J* = 7.0, 2.0, 1.0)	1.50 (dd, *J* = 7.0, 2.0 Hz)
19	5.47 (qt, *J* = 7.0, 1.0)	5.47 (d, *J* = 7.0 Hz)
21	3.31 (br. d, *J* = 15.0 Hz)	3.32 (d, *J* = 16.0 Hz)
21	3.86 (br. d, *J* = 15.0 Hz)	3.86 (d, *J* = 16.0 Hz)
NH	9.05 (br. s)	9.03 (br. s)

Table 26: Comparison of natural *vs.* synthetic conolidine by ^1H NMR analysis in $CDCl_3$. Diagnostic signals only for synthetic (*rac*)-conolidine. Biogenetic numbering is shown on (*rac*)-conolidine.[221]



rac-conolidine

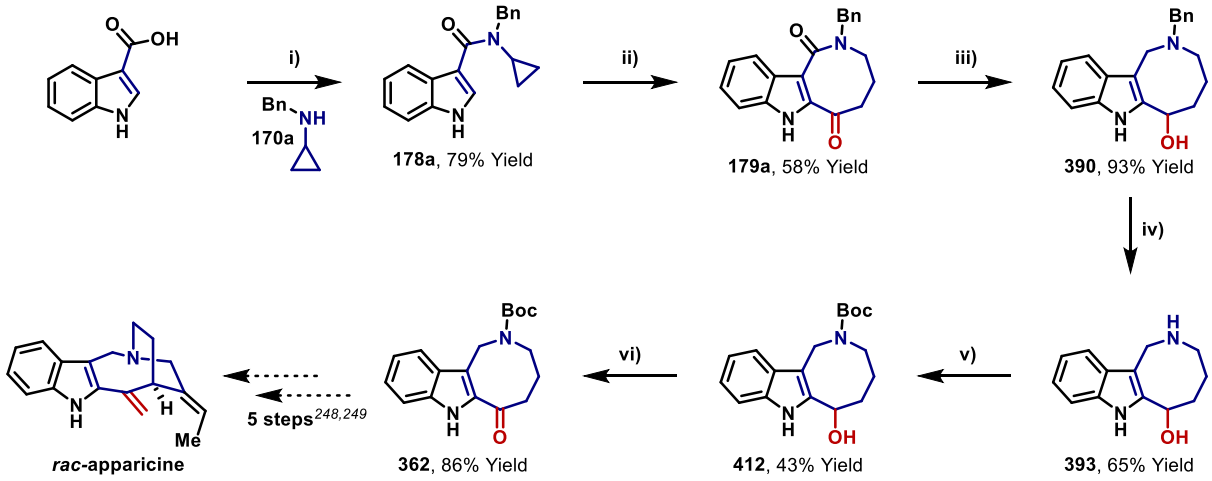
Carbon Number	Kam and coworkers[220] Natural (+)-conolidine ^{13}C NMR, 110 MHz, $CDCl_3$ ^{13}C (δ) ppm	This report Synthetic (*rac*)-conolidine ^{13}C NMR, 126 MHz, $CDCl_3$ ^{13}C (δ) ppm	Chemical Shift Difference Δδ
2	133.4	133.5	0.1
3	44.2	44.2	0.0
6	53.3	53.3	0.0
7	120.1	120.3	0.2
8	127.9	127.9	0.0
9	120.8	120.9	0.1
10	120.5	120.6	0.1
11	126.4	126.5	0.1
12	111.8	111.9	0.1
13	136.3	136.3	0.0
14	22.9	22.9	0.0
15	48.1	48.1	0.0
16	193.2	193.9	0.7[a]
18	12.7	12.8	0.1
19	122.9	123.0	0.1
20	130.2	130.3	0.1
21	55.0	55.1	0.1

Table 27: Comparison of natural *vs.* synthetic conolidine by ^{13}C NMR analysis in $CDCl_3$. Biogenetic numbering is shown on (*rac*)-conolidine.[221] [a] Micalizio reported a chemical shift of 193.4 ppm for C**16**[237] and Qi reported a chemical shift of 193.6 ppm for C**16**.[247]

Collectively, ^{1}H and ^{13}C NMR data provide compelling evidence for the formation of (*rac*)-conolidine; however, due to time constraints, no further work was carried out on this reaction. Consequently, future reaction development will focus on obtaining a pure sample for characterisation purposes. More significantly, these initial experiments provide proof-of-principal for a Ni(0)-catalysed α-vinylation to construct the azabicyclo[4.2.2]decane core and an impetus to conduct further studies. The major side reaction pathway identified was elimination of HI to form the corresponding propargylic amine **411**. Therefore, to side-step this obstacle, deprotonation of keto **406** should be performed at lower temperature (-40 °C) and with slow addition of base, prior to the addition of the Ni-catalyst. The ultimate goal for this process would be to render it asymmetric so as either enantiomer of conolidine would be accessible.

5.3 Formal synthesis of (*rac*)-apparicine

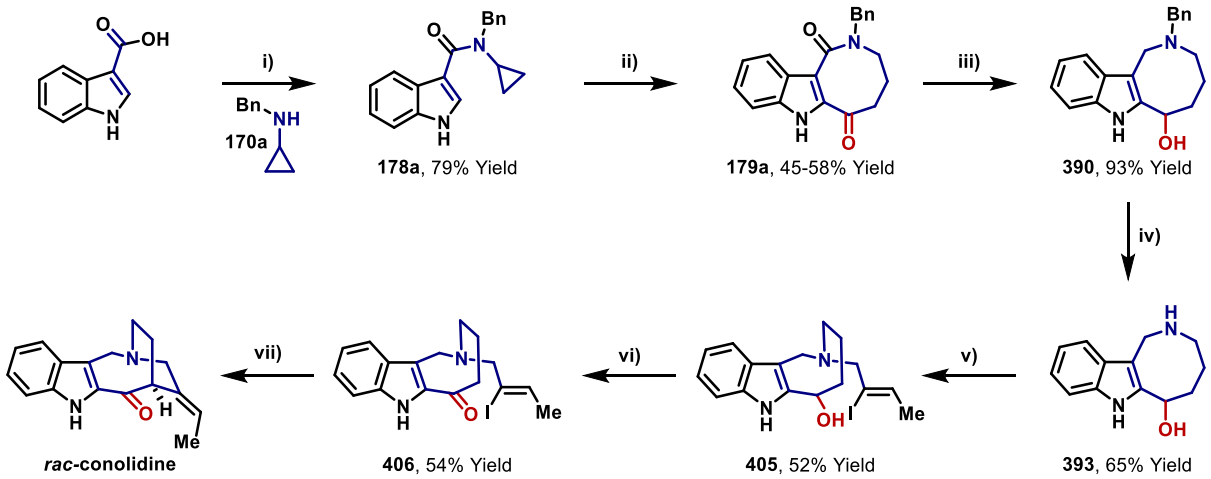
In parallel studies, it was anticipated that the Rh(I)-catalysed carbonylation protocol could be showcased in the formal synthesis of (*rac*)-apparicine through the elaboration of cyclisation product **179a** to known intermediate **362**. As previously discussed in Section 5.1.3, the total synthesis of apparicine was first accomplished by Bennasar and co-workers in 2011 (Scheme 100).[249,250] To this end, the formal synthesis of (*rac*)-apparicine was completed in 11 steps from known starting materials (Scheme 129). Versatile intermediate **179a** was advanced to secondary amine **393** in two steps (see Section 5.2.4.2 and Section 5.2.4.3) and the formal synthesis of (*rac*)-apparicine was concluded by *N*-Boc protection of amine **393** to give *N*-Boc **412**, followed by MnO_2 mediated oxidation to afford **362**. It should be noted the *N*-debenzylation and Boc protection have the potential to be carried out in one pot, thereby eliminating a synthetic step.



Scheme 129: Formal synthesis of (*rac*)-apparicine. *Reagents and conditions*: i) EDCI, DMAP, CH_2Cl_2, r.t., 16 h, 79%; ii) $[Rh(cod)OMe]_2$ (3.75 mol%), $P(4\text{-}FC_6H4)_3$ (22.5 mol%), $2\text{-}NO_2C_6H_4CO_2H$ (150 mol%), CO (1 atm), PhCN (0.3 M), 130 °C, 72 h, 58%; iii) $LiAlH_4$, THF, 0 °C to 80 °C, 24 h, 93%; iv) $Pd(OH)_2/C$, H_2, EtOH, r.t., 18 h, 65%; v) Boc_2O, DMF, r.t., 18 h, 43%; vi) MnO_2, acetone, r.t., 3 h, 86%.

5.4 Summary and conclusions from the studies in Chapter 5

In summary, the total synthesis of (*rac*)-conolidine has been accomplished by a concise 7-step synthetic route (Scheme 130) and the formal synthesis of (*rac*)-apparicine has been achieved in 11 synthetic steps from known amine **362** (Scheme 129). Central to the success of both syntheses was the Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **178a** to generate versatile *N*-heterocycle **179a**, which thereby validates the carbonylative ring expansion of cyclopropylamides to assemble the 8-membered C-ring of C5-nor stemmadenine natural products.

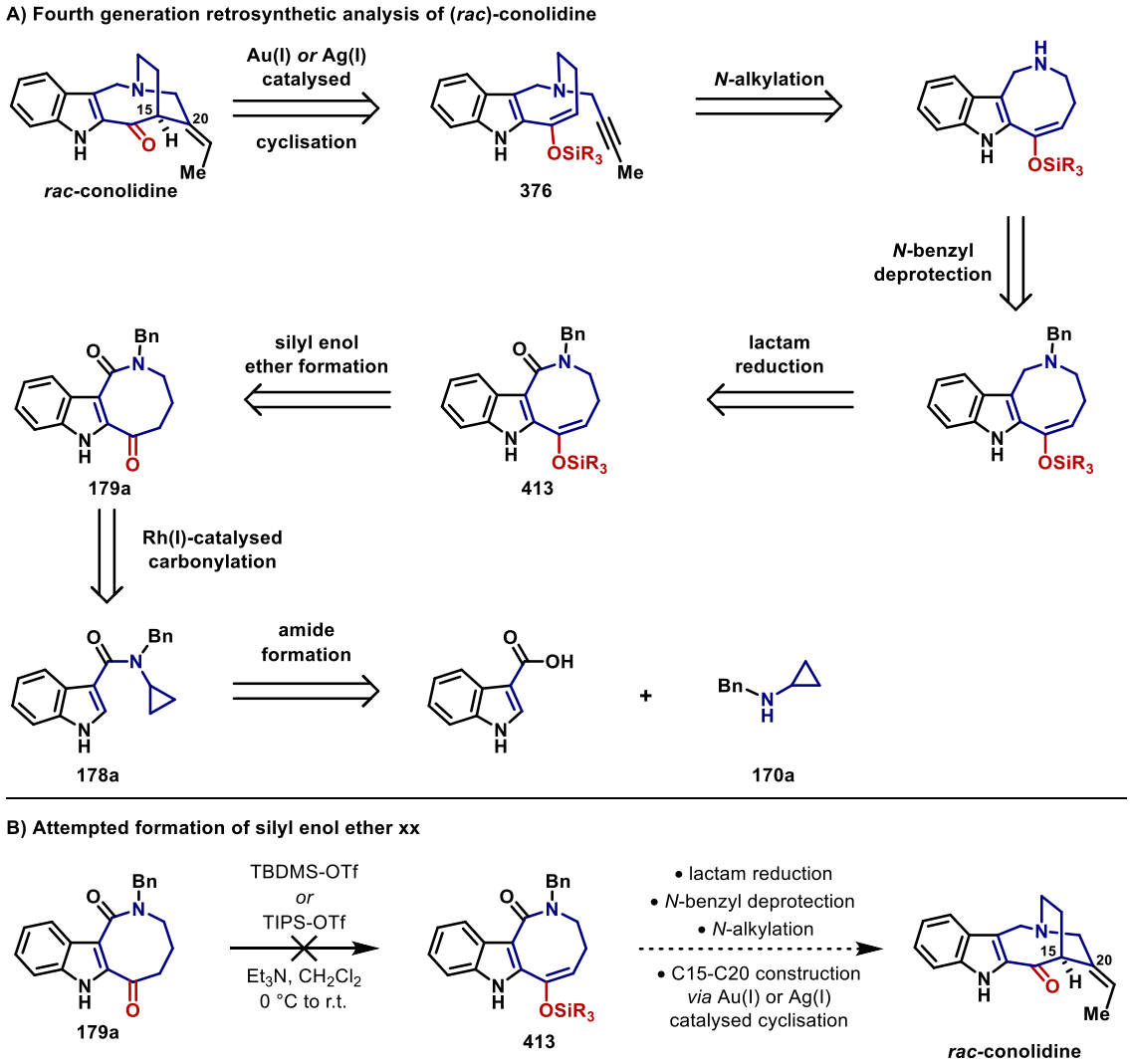


Scheme 130: Total synthesis of (*rac*)-conolidine. *Reagents and conditions*: i) EDCI, DMAP, CH_2Cl_2, r.t., 16 h, 79%; ii) $[Rh(cod)OMe]_2$ (3.75 mol%), P(4-$FC_6H4)_3$ (15.0 mol%), 2-$NO_2C_6H_4CO_2H$ (150 mol%), CO (3 bar, ChemSCAN II®), PhCN (0.3 M), 130 °C, 24 h, 45% *or* $[Rh(cod)OMe]_2$ (3.75 mol%), P(4-$FC_6H4)_3$ (22.5 mol%), 2-$NO_2C_6H_4CO_2H$ (150 mol%), CO (1 atm), PhCN (0.3 M), 130 °C, 72 h, 58%; iii) $LiAlH_4$, THF, 0 °C to 80 °C, 24 h, 93%; iv) $Pd(OH)_2$/C, H_2, EtOH, r.t., 18 h, 65%; v) tosylate **364**, DMF, K_2CO_3, r.t., 18 h, 52%; vi) MnO_2, acetone, r.t., 16 h, 54%; vii) $Ni(cod)_2(PCy_3)_2$, LiHMDS, THF, 0 °C to 50 °C, 18 h, <5%.

With regards to the total synthesis of (*rac*)-conolidine, first and second generation synthetic strategies were plagued by competing side reactions of substrates **178g** and **178i** in the Rh(I)-catalysed carbonylative cyclisation (Schemes 104 and 108). These challenges proved insurmountable and consequently led to a revised synthesis, in which cyclopropylamide **178a** was identified as a viable alternative. The existing conditions for the carbonylative cyclisation of **178a** were re-examined in order to provide sufficient quantities of lactam **179a** for subsequent steps. This in turn led to carbonylative cyclisation of **178a** being performed at 3 bar of CO in a ChemSCAN II© reactor. Extensive investigations into the conversion of lactam **179a** to penultimate intermediate **406** identified that a suitable order of manipulations was; (1) global $LiAlH_4$ reduction of **179a** which proceeded in excellent yield; (2) hydrogenative removal of the *N*-benzyl group of **390** with $Pd(OH)_2$; (3) *N*-alkylation of amine **393** with tosylate **364** and (4) MnO_2 mediated oxidation of alcohol **405**. Whilst these transformations were reliable, further development is needed to improve the overall efficiency. Specifically, the post-cyclisation transformations of **179a** required several functional group interconversions and redox manipulations that ideally would be erased. However, with access to key late-stage compound **406** established, exploratory investigations into the critical closure of the bridged piperidine ring were conducted. Several catalytic methods for this transformation were investigated and without doubt, this was the greatest synthetic challenge of the project. Of note, it was discovered that Pd(0)-catalytic systems proved unsuitable due to competing β-hydride pathways**,** which led to the isolation of [4.2.1]-bicyclic amine **407**. Conversely, a Ni(II) pre-catalyst was successfully employed to install the final C–C bond of the natural product. Though attempts to isolate an analytic sample of (*rac*)-conolidine failed,

NMR data on partially purified material provides convincing evidence for its formation. Going forward, future studies must prioritise isolating a clean sample of (*rac*)-conolidine. Additionally, if the Ni(0)-catalysed enolate coupling of vinyl iodide **406** could be rendered asymmetric, then this important molecule could be obtained in high enantiomeric purity. Without a doubt, exciting times lie ahead.

Furthermore, as outlined in Section 5.2.2, it was considered that the azabicyclo[4.2.2]decane core of (*rac*)-conolidine could be assembled by a Au(I) or Ag(I)-catalysed cyclisation of **376** (see Scheme 106). However, work on this particular route was impeded by failure to evoke Rh(I)-catalysed carbonylative cyclisation of amide **178i** that possessed a pre-installed *N*-alkynyl component (see Scheme 108). Building upon the post cyclisation transformations discussed in Section 5.2.4, it was postulated that the *N*-benzyl group of **179a** could be removed and replaced with an alkyne fragment. With this strategy in mind, a fourth generation retrosynthetic analysis of (*rac*)-conolidine is provided in Scheme 131.



Scheme 131: Fourth generation retrosynthetic analysis of (*rac*)-conolidine and attempted formation of silyl enol ether **413**

Brief attempts to form silyl enol ether **413** were met with difficulty due to silyl enol ether hydrolysis, competing *N*-silylation and degradation which precluded investigations into a Au(I) or Ag(I)-catalysed cyclisation (Scheme 131B). A literature survey was conducted to help identify suitable conditions, but no examples existed at the time that didn't first involve protecting the nitrogen atom of the indole unit.[342] Indeed, Li has previously commented that indole *N*-protection was essential for silyl enol ether formation[256] but for understandable reasons, we were against installing and then removing additional protecting groups. During the work reported here, Qi reported similar difficulties, but overcame these difficulties by employing 2,6-ludtidine as the base for a related substrate (see Scheme 98).[247] Accordingly, these conditions will be examined in future investigations as the successful realisation of this strategy may, in turn, avoid unnecessary redox fluctuations. What is more, this overall strategy has the potential to be asymmetric through the use of chiral gold complexes in the final C–C bond forming step.[246] Without a doubt, exciting times lie ahead.

Chapter 6 – Overall summary and conclusion

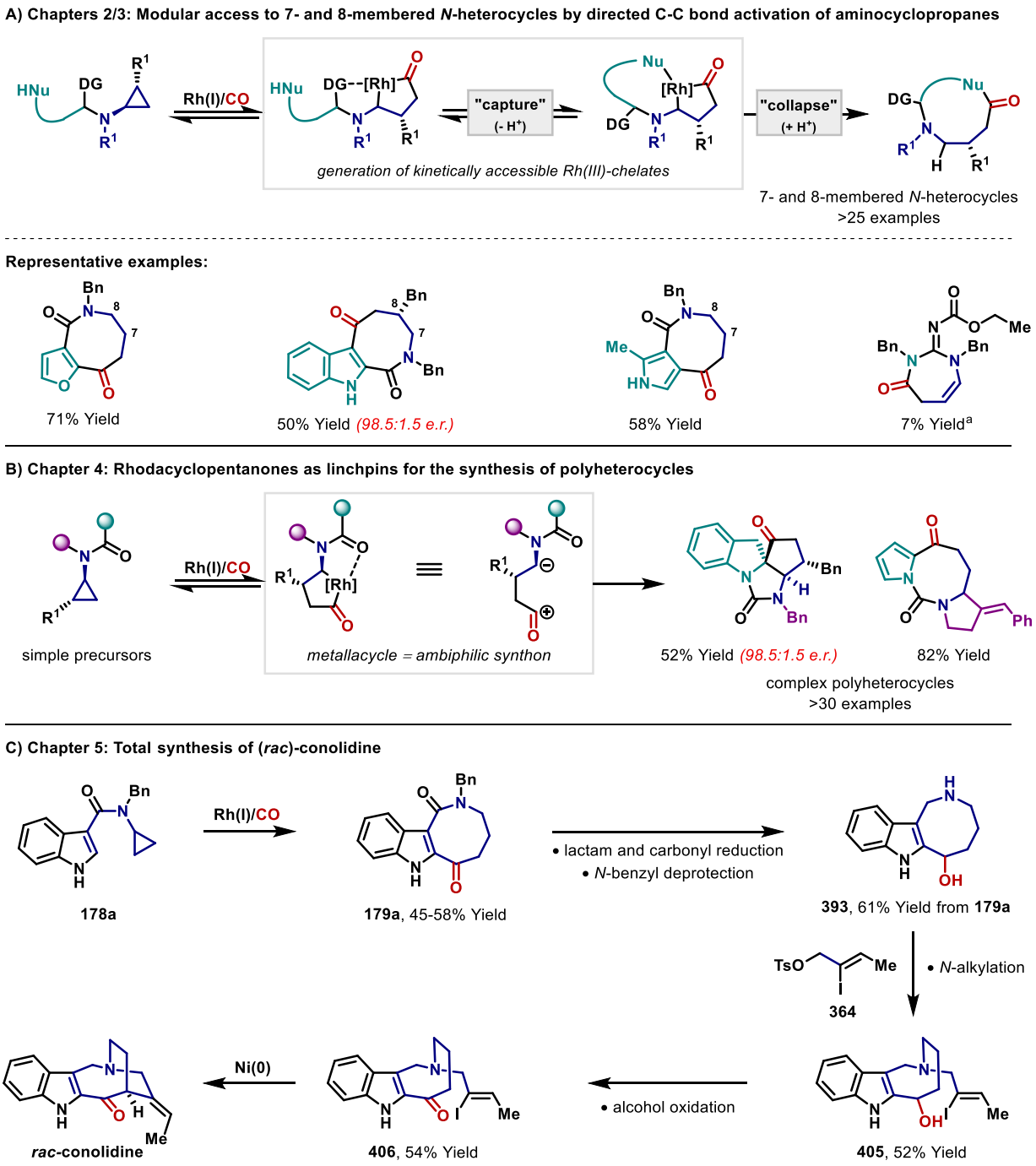
The research presented in this thesis has contributed to a growing body of processes that exploit catalytic C–C bond cleavage of small ring systems to access underexplored regions of chemical space. In Chapter 2, the scope of the Rh(I)-catalysed "capture-collapse" heterocyclisation was extended to include electron-rich cyclopropylamides, which enabled flexible access to a range of 8-membered *N*-heterocycles (Scheme 132A). Extensive optimisation of reaction conditions and the employment of 2-$NO_2C_6H_4CO_2H$ or (*E*)-$(CHCOOH)_2$ were needed to achieve high selectivity for the C7/8 saturated heterocycles. Overall, the success of this strategy hinges on the electrophilicity of rhodacyclopentanones and a metallacyclic templating effect to overcome the enthalpic and entropic barriers associated with challenging medium-sized ring closures. Attempts to expand the methodology to systems with electron-neutral/poor aromatic units and to systems that generate ≥8-membered *N*-heterocycles were unsuccessful; however, the development of related protocols remains an area of interest within the Bower group.

In Chapter 3, additional investigations into generality of the "capture-collapse" strategy led to the discovery of a second protocol, whereby cyclopropyl guanidine **263** underwent Rh(I)-catalysed carbonylative cyclisation to deliver 7-membered cyclic guanidine **264'**, albeit in poor yield (Scheme 132). Taken on balance, the widespread adoption of this strategy has been met with limited success due to the challenges associated with rhodacyclopentanone stability. Preliminary investigations into the synthesis of γ-lactam adduct **174b** by carbonylative ring expansion of secondary aminocyclopropanes **171b** were also described, and these results provide the basis for further studies.

Alongside G.-W. Wang and T. Young, subsequent studies in Chapter 4 focussed on the design of tailored aminocyclopropane substrates to achieve intricate Rh(I)-catalysed polycyclisation cascades. This led to the development of a unique indole dearomatisation protocol and polycyclisations that incorporate challenging medium-ring formations (Scheme 132B). For the former, deuterium exchange experiments and computational studies suggest that the mechanistic pathway involves $C(sp^2)$–$C(sp^2)$ reductive elimination and stereoretentive protodemetallation of an alkyl-Rh(I) species. In broader terms, these results show for the first time that rhodacyclopentanones can be effectively used as a linchpin technology for the assembly of various polyheterocyclic targets that are challenging or inaccessible using conventional methods.

The power and synthetic utility of the Rh(I)-catalysed "capture-collapse" heterocyclisation developed in Chapter 2 was successfully showcased in a total synthesis of (*rac*)-conolidine and a formal synthesis of apparicine. Significantly, the newly developed route to (*rac*)-conolidine proceeds in 7-steps from known amine **170a** and features a number of key transformations, including; (1) Rh(I)-catalysed carbonylative cyclisation of cyclopropylamide **178a** to construct the 8-membered C-ring; (2) a suite of

carefully orchestrated post-cyclisation steps of lactam **179a**, and (3) a Ni(0)-catalysed enolate coupling of vinyl iodide **406** to assemble the natural product's azabicyclo[4.2.2]decane core (Scheme 132C). It is expected that the lessons learned from these studies, including late-stage manipulations and various undesired setbacks, should inform and guide future forays towards conolidine and other challenging C5-nor stemmadenine natural products.



Scheme 132:A summary of the Rh(I)-catalysed processes described in this thesis and application to the total synthesis of (*rac*)-conolidine. [a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.

To conclude, this thesis outlines the development of several Rh(I)-catalysed processes that enable expeditious access to a wide range of sp^3-rich, medium-sized and pharmaceutically relevant (poly)heterocycles. These processes are enabled by the regioselective and efficient generation of versatile rhodacyclopentanones which are accessed *via* a step and atom economical reaction design. Given the ease with which molecular complexity is generated by the processes developed here, it is likely these new methodologies will find utility in synthetic and medicinal chemistry. In this regard, the synthesis of (*rac*)-conolidine validates the use of carbonylative ring expansion of cyclopropylamides in natural product synthesis.

Chapter 7 – Experimental procedures

7.1 General Experimental Details

Starting materials sourced from commercial suppliers (Acros, Sigma, Alfa Aesar, Fluorochem, Strem and TCI) were used as received unless otherwise stated. All reagents requiring purification were purified using standard laboratory techniques according to methods published by Perrin, Armarego, and Perrin (Pergamon Press, 1966). Anhydrous solvents, where necessary, were obtained by distillation using standard procedures or by passage through drying columns supplied by Anhydrous Engineering Ltd. Anhydrous PhCN was purchased as anhydrous grade and stored over activated 4Å molecular sieves prior to use. 1,2-DCB was distilled over CaH_2 and stored over activated 4Å molecular sieves under nitrogen. Petrol refers to the fraction of petroleum ether boiling in the range of 40–60 °C. The removal of solvents *in vacuo* was achieved using both a Büchi rotary evaporator (bath temperatures up to 45 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump). Materials were then dried on a high-vacuum line prior to analysis. Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon, using Schlenk techniques and flame/oven-dried equipment. In particular, catalytic reactions were carried out in oven dried (minimum 2 hours) or flame dried glass reaction tubes equipped with a Suba-Seal® and a balloon of inert gas (or carbon monoxide in the case of carbonylation reactions); liquid reagents, solutions or solvents were added *via* syringe through rubber septa; solid reagents were added *via* Schlenk type adapters. Commercially available Merck Kieselgel 60 F_{254} aluminium backed plates were used for TLC analysis. Visualisation was achieved by either UV fluorescence, basic $KMnO_4$ solution and heat. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). The crude material was applied to the column as a solution in CH_2Cl_2 or by pre-adsorption onto silica, as appropriate. Melting points were determined using a Reichert melting point table and temperature controller and are uncorrected. Infra-red spectra were recorded in the range 4000-600 cm^{-1} on a Perkin Elmer Spectrum either as neat films or solids compressed onto a diamond window. Abbreviations used are: w (weak), m (medium), s (strong) or br. (broad). NMR spectra were recorded using either a Varian 400-MR, Varian VNMR S500, Bruker Nano 400, JEOL ECS 300 or Bruker Advance III HD 500 Cryo. ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz as stated. ^{13}C NMR spectra were recorded at 101 MHz or 126 MHz as stated. Chemical shifts (δ) are quoted in parts per million (ppm), coupling constants (*J*) are given in Hz to the nearest 0.5 Hz. Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), septets (sept), heptets (hept), multiplets (m) and broad (br.). ^{1}H and ^{13}C NMR spectra were referenced to the appropriate residual solvent peak. ^{19}F spectra were referenced to CCl_3F as an external standard. Assignments of ^{1}H NMR and ^{13}C NMR signals were made, where possible, using COSY, HMQC, HMBC, and NOE experiments. Where mixtures of isomers (e.g. diastereomers and/or rotamers) have been characterized together, they are referred to as *A* and *B*. *Numbering systems for NMR signal assignments are specified on the structure*

and are not related to those used for the compound names. NMR yields were determined by employing 1,4-dinitrobenzene as an internal standard. Mass spectra were determined by the University of Bristol mass spectrometry service by electron impact (ESI^+) using a Bruker Daltonics FT-ICR-MS Apex 4e 7.0T FT-MS. Chiral SFC was performed using the racemate as a standard on an Agilent 1290 Infinity system equipped with a quaternary pump, diode array detector and column thermostat under the conditions specified in each case. Optical rotations were measured using an ADP440+ polarimeter at the concentration and temperature stated.

7.2 General Procedures

General Procedure A: Amine and indole carboxylic acid couplings

To a suspension of the specified carboxylic acid (100 mol%) in CH_2Cl_2 (0.3 M) at room temperature was added EDCI (110 mol%), DMAP (10 mol%) and the specified amine (105 mol%). The resulting solution was stirred at room temperature until the formation of a precipitate was observed. The precipitate was collected by vacuum filtration and washed with ice cooled CH_2Cl_2. The crude product was recrystallised, under the conditions noted, to afford the title compound.

General Procedure B: Amine and carboxylic acid couplings

To a suspension of the specified carboxylic acid (100 mol%) in CH_2Cl_2 (0.3 M) at room temperature was added EDCI (110 mol%), DMAP (10 mol%) and *N*-benzylcyclopropanamine (100–105 mol%). The resulting solution was stirred at room temperature for 18 hours. 1 M aqueous HCl (5 mL/mmol) was added and the solution was extracted with CH_2Cl_2 (2 × 3 mL/mmol). The organic extracts were combined, washed with water (5 mL/mmol), brine (5 mL/mmol), dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography, under the conditions noted to afford the title compound.

General procedure C: Rh(I)-catalysed carbonylative cyclisation of cyclopropylamides

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)OMe]_2$ (3.75 mol%), $P(4\text{-}(F)C_6H_4)_3$ (22.5 mol%), 2-nitrobenzoic acid (150 mol%) and the appropriate amide substrate (100 mol%). The tube was fitted with a rubber septum and purged with argon for 20 minutes. The reagents were dissolved in argon sparged anhydrous PhCN (0.3 M). The reaction vessel was purged with CO for approximately 10 minutes and the suspension was subsequently sparged with CO for approximately 30 seconds. The reaction was heated at the specified temperature (130–140 °C) under a CO atmosphere (1 atm) for the time noted. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography, under the conditions noted, to yield the target heterocycle.

General Procedure D: Hydrolysis of esters

To a solution of the appropriate cyclopropyl ester (100 mol%) in MeOH (0.4 M) at room temperature was added 4 M aq. NaOH (500 mol%). The mixture was stirred for 18 h before being concentrated *in vacuo.* Water (5 mL/mmol) and Et_2O (5 mL/mmol) were added and the layers separated. The aqueous portion was adjusted to pH 2 by addition of 2 M aq. HCl and then extracted with Et_2O (5 mL/mmol). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to afford the target carboxylic acid.

General procedure E: Deprotection/reductive amination of Boc-protected cyclopropylamines

To a solution of the specified Boc-protected cyclopropylamine (100 mol%) in CH_2Cl_2 (1 M) was added trifluoroacetic acid (1000 mol%) and the reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*, water (5 mL/mmol) was added and the solution was extracted with CH_2Cl_2 (5 mL/mmol). The aqueous portion was adjusted to pH 12 by addition of 2 M aq. NaOH and then extracted with CH_2Cl_2 (3 × 3 mL/mmol). The organic extracts were combined, dried over Na_2SO_4, concentrated *in vacuo* and the residue was dissolved in MeOH (0.5 M). $NaHCO_3$ (400 mol%) and benzaldehyde (95 mol%) were added and the solution was refluxed for 18 h. The reaction mixture was cooled to 0 °C and $NaBH_4$ (125 mol%) was added portion-wise over 10 minutes. The reaction was warmed to room temperature, stirred for 18 h and then concentrated *in vacuo*. Sat. aq. $NaHCO_3$ (10 mL/mmol) and CH_2Cl_2 (5 mL/mmol) were added, the layers were separated and the aqueous portion was further extracted with CH_2Cl_2 (2 × 5 mL/mmol). The organic extracts were combined, washed with brine (5 mL/mmol), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography, under the conditions noted, to afford the title compound.

General Procedure F: Rh(I)-catalysed carbonylative cyclisation of cyclopropylamides

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)OMe]_2$ (3.75 mol%), fumaric acid (100–150 mol%) and substrate (100 mol%). Anhydrous benzonitrile (1.0–0.67 M) was added by syringe and the tube was fitted with a rubber septum and purged with argon. The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The mixture was then heated at the specified temperature, under a CO atmosphere (1 atm), for the specified reaction time. The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography under the conditions noted to afford the desired product.

General Procedure G: Protection of indole or pyrrole derivatives with carbamoyl chloride derivatives

A flame-dried round-bottomed flask was charged with NaH (60% dispersion in mineral oil, 120 mol%) and this was suspended in THF (1.0 M) under nitrogen. The suspension was cooled to 0 °C and a

solution of indole or pyrrole derivative (100 mol%) in THF (0.5 M) was added dropwise over 10 minutes. The solution was stirred at 0 °C for 1 h, followed by dropwise addition of carbamoyl chloride derivative (110–150 mol%) in THF (0.5 M) over 10 minutes. The solution was then allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (3mL/mmol) and extracted with EtOAc (3 × 3mL/mmol). The organic extracts were combined, washed with brine (5mL/mmol), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography afforded the pure product.

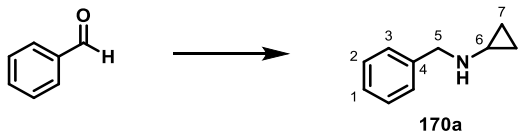
General Procedure H: Rh(I)-catalysed Carbonylative ring expansion of indole *N*-carbamoyl aminocyclopropanes

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (7.5 mol%), 4-(dimethylamino)benzoic acid (30 mol%), Na_2SO_4 (100 mol%) and the appropriate indole substrate (100 mol%). The tube was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (0.1 M) was added by syringe. The reaction vessel was sparged with CO for approximately 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The mixture was then heated at 130 °C under an atmosphere of CO for 72 h. The mixture was cooled to room temperature, concentrated *in vacuo* and the residue was purified by flash column chromatography, under the conditions noted, to yield the target heterocycle.

7.3 Experimental procedures for the studies in Chapter 2

7.3.1 Synthesis of substrates and catalysis products

***N*-benzylcyclopropanamine (170a)**

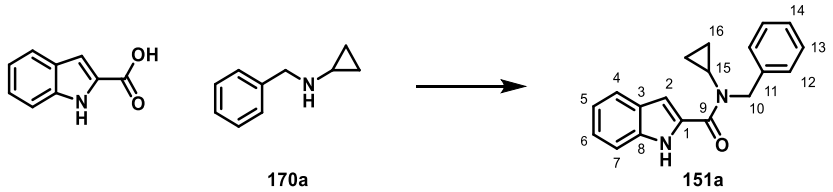


170a

A solution of benzaldehyde (4.10 mL, 40.0 mmol), cyclopropylamine (3.30 mL, 48.0 mmol) and $NaHCO_3$ (5.04 g, 60 mmol) in MeOH (40 mL) were refluxed for 16 hours. The resulting suspension was cooled to 0 °C and $NaBH_4$ (1.89 g, 50.0 mmol) was added portion wise over 10 minutes. The reaction was warmed to room temperature and stirred for an additional 16 hours. The reaction mixture was concentrated *in vacuo* before the addition of saturated aqueous $NaHCO_3$ (50 mL). The solution was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound **170a** (5.72 g, 98%) as a pale yellow oil. The crude material was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.20 (5H, m, 2 × C**2**-H, 2 × C**3**-H, C**1**-H), 3.84 (2H, s, C**5**-H_2), 2.15 (1H, tt, *J* = 6.5, 3.5 Hz, C**6**-

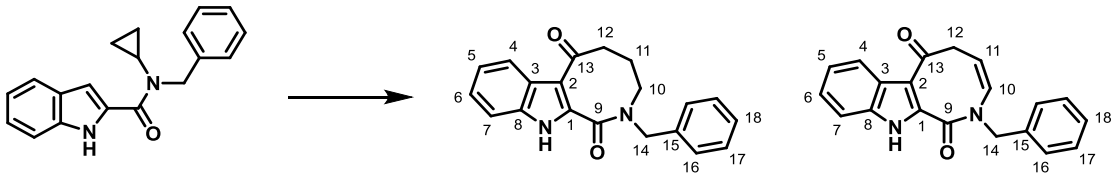
H), 1.81 (1H, br. s, NH), 0.49 – 0.33 (4H, m, 2 × C**7**-H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7 (C**4**), 128.5, 128.3, 127.0 (C**1**, C**2**, C**3**), 54.0 (C**5**), 30.2 (C**6**), 6.6 (C**7**). *The spectroscopic properties of this compound were consistent with the data available in literature.*[16]

***N*-Benzyl-*N*-cyclopropyl-1*H*-indole-2-carboxamide (151a)**



General Procedure A: 1*H*-Indole-2-carboxylic acid (1.61 g, 10.0 mmol) and *N*-benzylcyclopropylamine **170a** (1.54 g, 10.5 mmol) were employed to afford the title compound **151a** (2.30 g, 79%) as a colourless solid. The crude material was isolated with good purity and was used without further purification. m.p.: 207–208 °C (ethanol); ν_{max}/ cm^{-1}: 3271 (s), 3011 (m), 1602 (s), 1521 (s), 1433 (s), 1401 (s), 1347 (s), 1280 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.55 (1H, s, NH), 7.62 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.46 (1H, d, *J* = 8.5 Hz, C**7**-H), 7.39 – 7.11 (7H, m, C**2**-H, C**6**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.04 (1H, dd, *J* = 8.5, 8.0 Hz, C**5**-H), 4.79 (2H, s, C**10**-H$_2$), 3.05 (1H, m, C**15**-H), 0.93 – 0.60 (4H, m, 2 × **16**-H$_2$); ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.0 (C**9**), 138.5 (C**11**), 135.9 (C**8**), 130.6 (C**1**), 128.5 (C**13**), 127.1 (C**3**), 127.1 (C**12**), 126.9 (C**14**), 123.5 (C**6**), 121.7 (C**4**), 119.6 (C**5**), 112.1 (C**7**), 106.0 (C**2**), 50.6 (C**10**), 31.0 (C**15**), 10.1 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{18}N_2NaO$: 313.1331. Found [M + Na]$^+$: 313.1311.

2-Benzyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (152a) and **(*Z*)-2-Benzyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153a)**



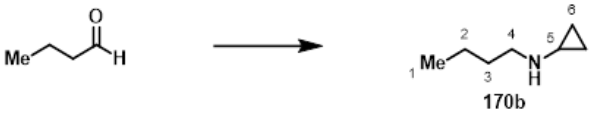
General Procedure C: Indole **151a** (43.5 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (75/15/10 % toluene/CH_2Cl_2/EtOAc) to yield the title compound **152a** (36.7 mg, 77%) as a colourless solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a >12:1 (**152a**:**152a**) mixture of products. The minor product **153a** was not isolated.

Data for major compound **152a**: m.p.: 209–211 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 3220 (br. m), 2926 (m), 1614 (br. s), 1577 (m), 1518 (s), 1423 (s), 1321 (s), 1141 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.48 (1H, br. s, NH), 8.49 (1H, m, C**4**-H), 7.46 – 7.27 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-

H), 4.91 (2H, s, C**14**-H$_2$), 3.69 (2H, br. m, C**10**-H$_2$), 2.86 (2H, br. m, C**12**-H$_2$), 2.01 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H$_2$); ^{1}H NMR (500 MHz, Acetonitrile-d_3, 65 °C) δ 10.34 (1H, br. s, NH), 8.50 (1H, d, *J* = 8.1 Hz, C**4**-H), 7.76 – 7.17 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 4.93 (2H, s, C**14**-H$_2$), 3.73 (2H, t, *J* = 6.5 Hz, C**10**-H$_2$), 2.84 (2H, t, *J* = 7.0 Hz, C**12**-H$_2$), 2.03 (2H, m, C**11**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.2 (C**13**), 164.5 (C**9**), 136.5 (C**15**), 135.3 (C**8**), 133.9 (C**1**), 129.0, 128.3, 128.1 (C**16**, C**17** and C**18**), 126.2 (C**3**), 125.4 (C**6**), 123.7, 123.6 (C**4** and C**5**), 118.2 (C**2**), 111.9 (C**7**), 49.8 (C**14**), 46.8 (C**10**), 39.0 (C**12**), 26.9 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{18}N_2NaO_2$: 341.1260. Found [M + Na]$^+$: 341.1270. *A ^{1}H NMR spectrum was recorded at 65 °C in Acetonitrile-d_3 because slow conformational interconversion gave broad signals at room temperature*.

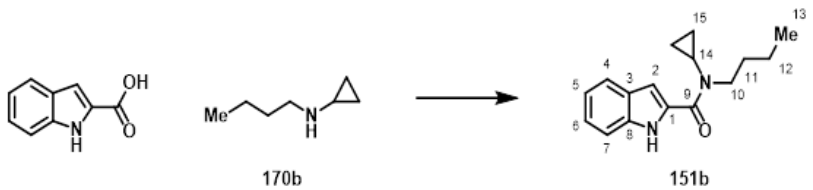
Data for minor compound **153a**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.80 (1H, m, C**11**-H).

***N*-Butylcyclopropanamine (170b)**



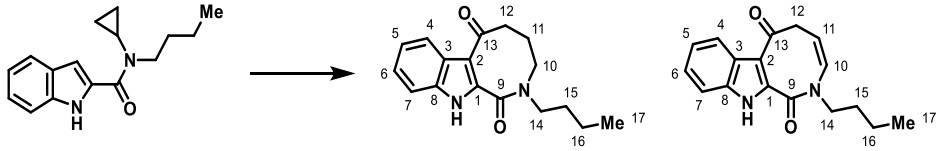
A solution of cyclopropylamine (4.16 mL, 60.0 mmol), butyraldehyde (4.51 mL, 50.0 mmol) and $NaHCO_3$ (6.30 g, 75.0 mmol) in MeOH (50 mL) was heated at reflux for 16 h. The reaction mixture was cooled to 0 °C and $NaBH_4$ (2.36 g, 62.5 mmol) was added portion wise over 5 minutes. The solution was warmed to r.t. and stirred for 6 h. The reaction mixture was concentrated *in vacuo* and then saturated aqueous $NaHCO_3$ (50 mL) was added. The solution was extracted with CH_2Cl_2 (3 × 50 mL) and then the organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to yield *N*-butylcyclopropylamine **170b** (3.82 g, 67%) as a yellow oil. *N.B. Due to volatility issues a cold water bath was used when concentrating in vacuo*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (2H, t, *J* = 7.0 Hz, C**4**-H$_2$), 2.10 (1H, tt, *J* = 6.5, 3.5 Hz, C**5**-H), 1.56 (H, br. s, NH), 1.46 (2H, m, C**3**-H$_2$), 1.38 – 1.27 (2H, m, C**2**-H$_2$), 0.91 (3H, t, *J* = 7.5 Hz, C**1**-H$_3$), 0.49 – 0.26 (4H, m, 2 × C**6**-H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.6 (C**4**), 32.3 (C**3**), 30.1 (C**5**), 20.6 (C**2**), 14.0 (C**1**), 6.5 (C**6**). *The spectroscopic properties of this compound are in agreement with the literature*.[20]

***N*-Butyl-*N*-cyclopropyl-1*H*-indole-2-carboxamide (151b)**



General Procedure A: 1*H*-indole-2-carboxylic acid (322 mg, 2.00 mmol) and *N*-butylcyclopropanamine **170b** (237 mg, 2.10 mmol) were employed. The crude residue was recrystallised from ethanol to afford the title compound **151b** as an off-white solid (350 mg, 68%); m.p.: 119–122 °C (ethanol); ν_{max}/ cm^{-1}: 3281 (br. s), 2954 (m), 2870 (m), 1593 (s), 1575 (s), 1402 (s), 1347 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (1H, br. s, NH), 7.67 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.45 (1H, d, *J* = 8.5 Hz, C**7**-H), 7.29 (1H, m, C**6**-H), 7.18 – 7.09 (2H, m, C**1**-H and C**5**-H), 3.67 (2H, t, *J* = 7.5 Hz, C**10**-H_2), 3.07 (1H, tt, *J* = 7.0, 4.0 Hz, C**14**-H), 1.71 (2H, tt, *J* = 7.5, 7.5 Hz, C**11**-H_2), 1.44 – 1.34 (2H, m, C**12**-H_2), 1.04 – 1.00 (2H, m, 1 × C**15**-H_2), 0.97 (3H, t, *J* = 7.5 Hz, C**13**-H_3), 0.85 – 0.77 (2H, m, 1 × C**15**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.4 (C**9**), 135.6 (C**8**), 130.6 (C**1**), 128.0 (C**3**), 124.4 (C**6**), 122.2 (C**4**), 120.3 (C**5**), 111.9 (C**7**), 106.8 (C**2**), 47.8 (C**10**), 30.9 (C**14**), 30.4 (C**11**), 20.4 (C**12**), 14.0 (C**13**), 11.0 (C**15**); HRMS: $(ESI)^+$ Calculated for $C_{16}H_{21}N_2O$: 257.1648. Found $[M + H]^+$: 257.1660.

2-Butyl-2,3,4,5-tetrahydro-1H-azocino[3,4-b]indole-1,6(11H)-dione (152b) and **(Z)-2-Butyl-2,5-dihydro-1H-azocino[3,4-b]indole-1,6(11H)-dione (153b)**

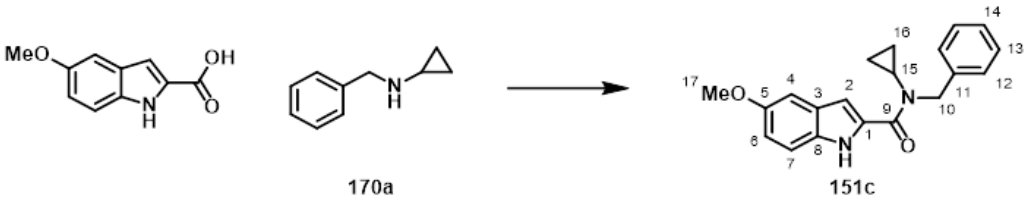


General Procedure C: Indole **151b** (25.6 mg, 0.10 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (10–35 % EtOAc/pentane) to yield the title compound **152b** (12.5 mg, 44%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 6:1 (**152b**:**153b**) mixture of products. The minor product **153b** was not isolated.

Data for major compound **152b**: ν_{max}/ cm^{-1}: 3264 (br. s), 2923 (m), 1642 (s), 1616 (s), 1520 (s), 1424 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (1H, s, NH), 8.49 (1H, dd, *J* = 7.0, 2.0 Hz, C**4**-H), 7.44 (1H, dd, *J* = 7.0, 2.0 Hz, C**7**-H), 7.38 – 7.28 (2H, m, C**5**-H and C**6**-H), 3.70 (2H, br. m, C**10**-H_2), 3.61 (2H, br. m, C**14**-H_2) 2.87 (2H, br. m, C**12**-H_2), 2.13 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H_2), 1.70 (2H, tt, *J* = 7.5, 7.5 Hz, C**15**-H_2), 1.42 (tq, *J* = 7.5, 7.5 Hz, C**16**-H_2), 0.98 (3H, t, *J* = 7.5 Hz, C**17**-H_3); ^{13}C NMR (101 MHz $CDCl_3$): δ 196.3 (C**13**), 163.9 (C**9**), 134.5 (C**8**), 129.2 (C**1**), 126.2 (C**3**), 125.4 (C**6**), 123.8, 123.7 (C**4** and C**5**), 118.2 (C**2**), 111.7 (C**7**), 47.4, 47.1 (C**10** and C**14**), 38.9 (C**12**), 30.2 (C**15**), 27.5 (C**11**), 20.5 (C**16**), 14.0 (C**17**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{21}N_2O_2$: 285.1598. Found $[M + H]^+$: 285.1604.

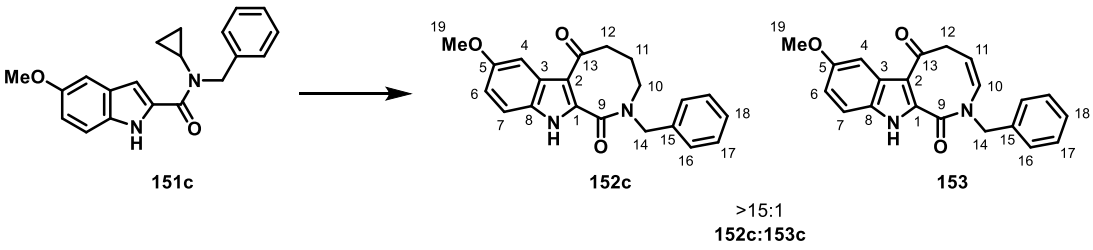
Data for minor compound **153b**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.75 (1H, m, C**11**-H).

***N*-Benzyl-*N*-cyclopropyl-5-methoxy-1*H*-indole-2-carboxamide (151)**



General Procedure A: 5-Methoxy-1*H*-indole-2-carboxylic acid (382 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed. The crude residue was recrystallised from ethanol to afford the title compound **151c** (420 mg, 66%) as an off-white solid; m.p.: 200–202 °C (ethanol); ν_{max}/ cm^{-1}: 3255 (s), 1602 (s), 1520 (s), 1412 (s), 1401 (s), 1277 (s), 1163 (s), 1027 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (1H, br. s, NH), 7.36 – 7.23 (6H, m, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.08– 7.06 (2H, m, C**2**-H and C**4**-H), 6.96 (1H, dd, *J* = 9.0, 2.5 Hz, C**6**-H), 4.88 (2H, s, C**10**-H_2), 3.84 (3H, s, C**17**-H_3), 2.99 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 1.03 – 0.81 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.7 (C**9**), 154.6 (C**5**), 138.2 (C**11**), 131.2 (C**8**), 130.7 (C**1**), 128.8, 128.3, 127.6, 127.4 (C**3**, C**12**, C**13** and C**14**), 116.2 (C**6**), 112.8 (C**7**), 106.8 (C**2**), 102.6 (C**4**), 55.9 (C**17**), 51.9 (C**10**), 31.4 (C**15**), 10.9 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{21}N_2O_2$: 321.1598. Found [M + H] $^+$: 321.1613.

2-Benzyl-8-methoxy-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (152c) and **(Z)-2-Benzyl-8-methoxy-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153c)**



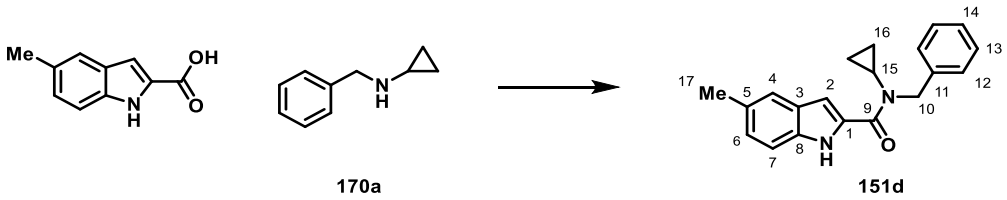
General Procedure C: Indole **151c** (48.0 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (70/15/10%, toluene/CH_2Cl_2/EtOAc) to yield the title compound **152c** (35.0 mg, 67%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a >15:1 (**152c**: **153c**) mixture of products. The minor product **153c** was not isolated.

Data for major compound **152c**: m.p.: 212–217 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 3223 (br. m), 2933 (m), 1614 (br. s), 1585 (m), 1512 (s), 1492 (m), 1453 (s), 1422 (s), 1268 (s), 1204 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (1H, br. s, NH), 7.95 (1H, d, *J* = 2.5 Hz, C**4**-H), 7.44 – 7.27 (6H, m, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 6.95 (1H, dd, *J* = 9.0, 2.5 Hz, C**6**-H), 4.89 (2H, br. m, C**14**-H_2), 3.88 (3H, s, C**19**-H_3), 3.69 (2H, br. m, C**10**-H_2), 2.84 (2H, br. m, C**12**-H_2), 2.00 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.3 (C**13**), 164.5 (C**9**), 157.2 (C**5**), 136.6 (C**15**), 133.9 (C**1**), 130.4 (C**8**), 129.0, 128.3 (C**16** and C**17**), 128.1 (C**18**), 127.0 (C**3**), 118.0 (C**2**), 116.9 (C**6**), 112.9 (C**7**), 103.6 (C**4**), 55.8

(C**19**), 49.8 (C**14**), 46.8 (C**10**), 39.0 (C**12**), 26.9 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{21}H_{20}N_2NaO_3$: 371.1366. Found [M + Na]$^+$: 371.1384.

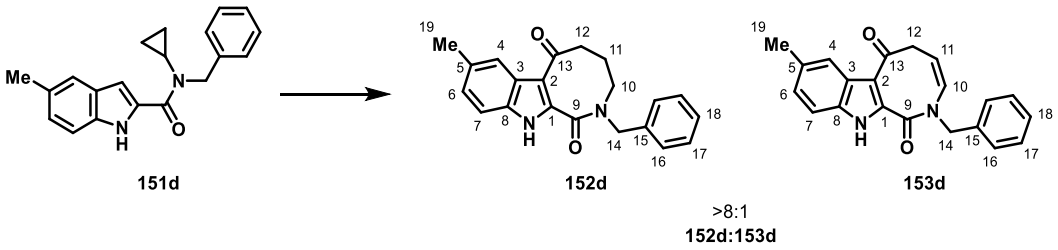
Data for minor compound **153c**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.80 (1H, m, C**11**-H).

***N*-Benzyl-*N*-cyclopropyl-5-methyl-1*H*-indole-2-carboxamide (151d)**



General Procedure A: 5-Methyl-1*H*-indole-2-carboxylic acid (350 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed. The crude residue was recrystallised from $CHCl_3$ to afford the title compound **151d** (415 mg, 68%) as an off-white solid; m.p.: 191–193 °C ($CHCl_3$); ν_{max}/ cm^{-1}: 3269 (s), 1601 (s), 1525 (m), 1431 (s), 1403 (s), 1277 (s), 1031 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (1H, br. s, NH), 7.44 (1H, m, C**4**-H), 7.37 – 7.23 (6H, m, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.11 (1H, dd, *J* = 8.5, 1.5 Hz, C**6**-H), 7.07 (1H, s, C**2**-H), 4.89 (2H, s, C**10**-H_2), 3.00 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 2.44 (3H, s, C**17**-H_3), 1.07 – 0.78 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.1 (C**9**), 138.5 (C**11**), 134.3 (C**8**), 130.5 (C**1**), 128.5 (C**13**), 128.1 (C**5**), 127.4 (C**3**), 127.1 (C**12**), 126.9 (C**14**), 125.4 (C**6**), 120.9 (C**4**), 111.8 (C**7**), 105.5 (C**2**), 50.6 (C**10**), 31.0 (C**15**), 21.2 (C**17**), 10.1 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{21}N_2O$: 305.1648. Found [M + H]$^+$: 305.1651.

2-Benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (152d) and **(*Z*)-2-Benzyl-8-methyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153d)**

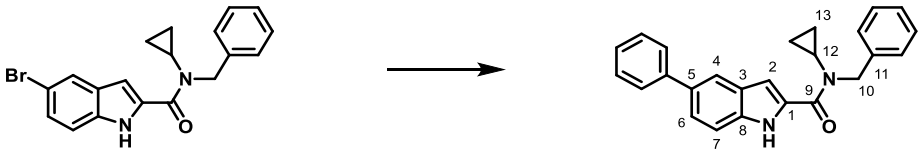


General Procedure C: Indole **151d** (45.6 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (10–30% EtOAc/pentane) to yield the title compound **152d** (27.8 mg, 56%) as an off-white solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 8:1 (**152d**:**153d**) mixture of products. The minor product **153d** was not isolated.

Data for major compound **152d**: m.p.: 195–197 °C ($CHCl_3$); ν_{max}/ cm^{-1}: 3226 (br. m), 2924 (m), 1610 (br. s), 1582 (m), 1516 (s), 1452 (s), 1440 (s), 1420 (s), 1218 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (1H, br. s, NH), 8.29 (1H, d, *J* = 1.5 Hz, C**4**-H), 7.38 – 7.29 (6H, m, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.14 (1H, dd, *J* = 8.5, 1.5 Hz, C**6**-H), 4.89 (2H, s, C**14**-H_2), 3.67 (2H, br. m, C**10**-H_2), 2.83 (2H, br. m, C**12**-H_2), 2.47 (3H, s, C**19**-H_3), 1.99 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.3 (C**13**), 164.6 (C**9**), 136.6 (C**15**), 133.9 (C**1**), 133.6 (C**5**), 133.5 (C**8**), 129.0, 128.3, 128.1 (C**16**, C**17** and C**18**), 127.3 (C**6**), 126.5 (C**3**), 123.1 (C**4**), 117.9 (C**2**), 111.5 (C**7**), 49.8 (C**14**), 46.7 (C**10**), 39.0 (C**12**), 26.9 (C**11**), 21.8 (C**19**); HRMS: $(ESI)^+$ Calculated for $C_{21}H_{21}N_2O_2$: 333.1598. Found $[M + H]^+$: 333.1594.

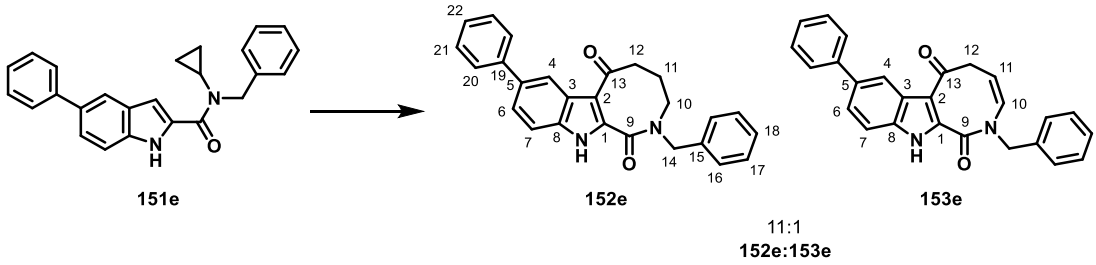
Data for minor compound **153d**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.80 (1H, m, C**11**-H).

***N*-Benzyl-*N*-cyclopropyl-5-phenyl-1*H*-indole-2-carboxamide (151e)**



To an oven dried reaction tube was added *N*-benzyl-5-bromo-*N*-cyclopropyl-1*H*-indole-2-carboxamide **151g** (184 mg, 0.50 mmol), phenylboronic acid (242 mg, 1.00 mmol), $Pd(PPh_3)_4$ (28.0 mg, 0.025 mmol) and K_2CO_3 (173 mg, 1.25 mmol). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in 1,4-dioxane/H_2O (3:1, 4.0 mL) The tube was sealed and heated at 105 °C for 4 hours and then cooled to room temperature. The reaction mixture was filtered through a pad of celite® and concentrated *in vacuo.* The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **151e** (130 mg, 71%) as a colourless solid; m.p.: 197–199 °C (ethanol); ν_{max}/ cm^{-1}: 3252 (m), 1604 (s), 1530 (m), 1493 (m), 1431 (m), 1403 (m), 1288 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.62 (1H, br. s, NH), 7.89 (1H, s, C**4**-H), 7.70 – 7.63 (2H, m, 2 × Ar-CH), 7.56 – 7.51 (2H, m, C**6**-H and C**7**-H), 7.47 – 7.43 (2H, m, 2 × Ar-CH), 7.41 – 7.21 (7H, m, C**2**-H and 6 × Ar-CH), 4.80 (2H, s, C**10**-H_2), 3.10 (1H, m, C**12**-H), 0.94 – 0.67 (4H, m, 2 × C**13**-H_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.9 (C**9**), 141.4 (C**5**), 138.4 (C**11**), 135.5 (C**8**), 132.1, 131.3 (Ar-C) 128.8, 128.5 (4 × Ar-CH), 127.7 (C**3**), 127.1, 126.9, 126.6, 126.4 (6 × Ar-CH), 123.1 (C**6**), 119.5 (C**4**), 112.6 (C**7**), 106.4 (C**2**), 50.6 (C**10**), 31.0 (C**12**), 10.1 (C**13**); HRMS: $(ESI)^+$ Calculated for $C_{25}H_{23}N_2O$: 367.1732. Found $[M + H]^+$: 367.1820.

2-Benzyl-8-phenyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (152e) and **(*Z*)-2-Benzyl-8-phenyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153e)**

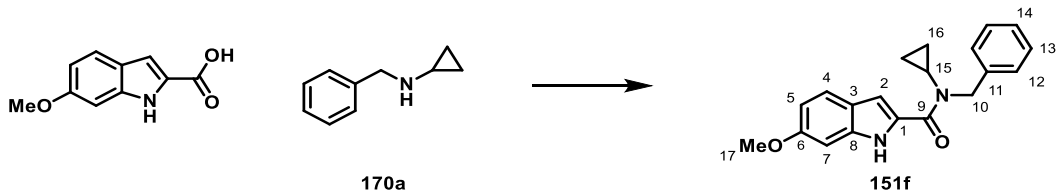


General Procedure C: Indole **151e** (55.4 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (10–35% EtOAc/pentane) to yield the title compound **152e** (41.7 mg, 70%) as an off white solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 11:1 (**152e**:**153e**) mixture of products. The minor product **153e** was not isolated.

Data for major compound **152e**: m.p.: 220–222 °C (CH_2Cl_2) ν_{max}/ cm^{-1}: 3240 (br. m), 2968 (m), 1615 (br. s), 1584 (m), 1528 (m), 1452 (m), 1419 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (1H, br. s, NH), 8.74 (1H, d, *J* = 1.5 Hz, C**4**-H), 7.72 – 7.64 (2H, m, 2 × C**20**-H), 7.56 (1H, dd, *J* = 8.5, 1.5 Hz, C**6**-H), 7.50 – 7.41 (3H, m, C**7**-H and 2 × C**21**-H), 7.40 – 7.28 (6H, m, 2 × C**16**-H, 2 × C**17**-H, C**18**-H and C**22**-H), 4.93 (2H, s, C**14**-H_2), 3.71 (2H, br. m, C**10**-H_2), 2.87 (2H, t, *J* = 7.5 Hz, C**12**-H_2), 2.02 (2H, tt, *J* = 7.5, 6.5 Hz, C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.2 (C**13**), 164.6 (C**9**), 141.9 (C**5**), 137.1 (C**19**), 136.5 (C**15**), 134.9 (C**8**), 134.4 (C**1**), 129.0 (C**17**), 128.8 (C**21**), 128.2 (C**16**), 128.1 (C**18**), 127.6 (C**20**), 126.9 (C**22**), 126.7 (C**3**), 125.3 (C**6**), 121.9 (C**4**), 118.5 (C**2**), 112.1 (C**7**), 49.9 (C**14**), 46.8 (C**10**), 39.0 (C**12**), 26.9 (C**11**); HRMS: (ESI)$^{+}$ Calculated for $C_{26}H_{23}N_2O_2$: 395.1754. Found [M + H]$^{+}$: 395.1761.

Data for minor compound **153e**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.81 (1H, m, C**11**-H).

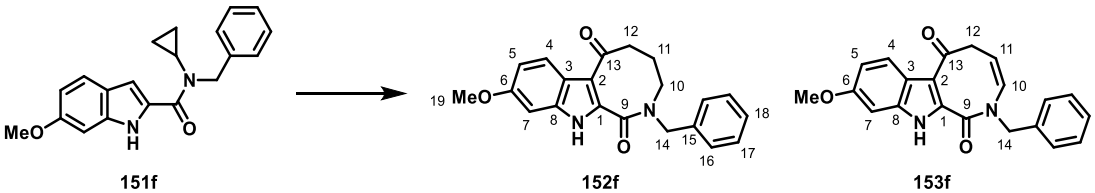
***N*-Benzyl-*N*-cyclopropyl-6-methoxy-1*H*-indole-2-carboxamide (151f)**



General Procedure A: 6-Methoxy-1*H*-indole-2-carboxylic acid (382 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed. The crude residue was recrystallised from $CHCl_3$ to afford the title compound **151f** as a yellow solid (400 mg, 63%); m.p.: 207–208 °C ($CHCl_3$); ν_{max}/ cm^{-1}: 3281 (br. s), 1625 (m), 1593 (s), 1575 (m), 1508 (m), 1417 (m), 1275 (s), 1230 (m), 1027 (m); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.35 (1H, br. s, NH), 7.49 (1H, d, *J* = 8.5

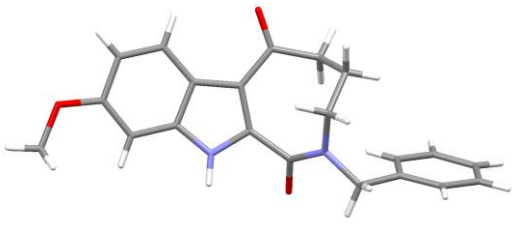
Hz, C**4**-H), 7.36 – 7.21 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.14 (1H, m, C**2**-H), 6.92 (1H, d, *J* = 2.5 Hz, C**7**-H), 6.70 (1H, dd, *J* = 8.5, 2.5 Hz, C**5**-H), 4.77 (2H, s, C**10**-H_2), 3.77 (3H, s, C**17**-H_3), 3.04 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 0.88 – 0.84 (2H, m, 1 × C**16**-H_2), 0.78 – 0.64 (2H, m, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.9 (C**9**), 157.2 (C**6**), 138.6 (C**11**), 136.9 (C**8**), 129.4 (C**1**), 128.4, 127.1 (C**12**, C**13**), 126.8 (C**14**), 122.5 (C**4**), 121.6 (C**3**), 111.0 (C**5**), 106.6 (C**2**), 93.9 (C**7**), 55.1 (C**17**), 50.5 (C**10**), 31.0 (C**15**), 10.2 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{21}N_2O_2$: 321.1598. Found [M + H] $^+$: 321.1599.

2-Benzyl-9-methoxy-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (152f) and **(*Z*)-2-Benzyl-9-methoxy-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153f)**



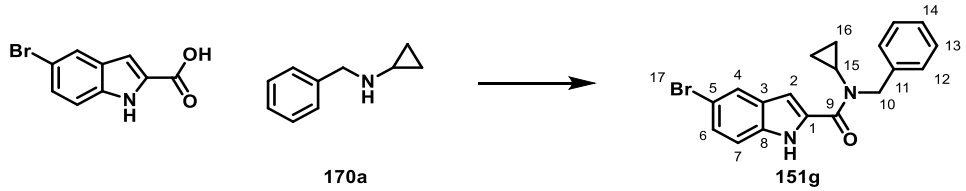
General Procedure C: Indole **151f** (48.0 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (10–40% EtOAc/pentane) to yield the title compound **152f** (23.5 mg, 45%) as a colourless solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed an 8:1 (**152f**:**153f**) mixture of products. The minor product **153f** was not isolated.

Data for major compound **152f**: m.p.: 192–195 °C ($CHCl_3$); ν_{max}/ cm^{-1}: 3239 (br. m), 2951 (m), 1606 (br. s), 1576 (m), 1517 (s), 1451 (m), 1410 (s), 1261 (s), 1232 (s), 1109 (s), 1028 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (1H, br. s, NH), 8.33 (1H, d, *J* = 9.0 Hz, C**4**-H), 7.42 – 7.27 (5H, m, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 6.94 (1H, dd, *J* = 9.0, 2.5 Hz, C**5**-H), 6.85 (1H, d, *J* = 2.5 Hz, C**7**-H), 4.90 (2H, s, C**14**-H_2), 3.76 (3H, s, C**19**-H_3), 3.68 (2H, br. m, C**10**-H_2), 2.83 (2H, br. m, C**12**-H_2), 1.99 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.4 (C**13**), 164.6 (C**9**), 158.7 (C**6**), 136.7, 136.3 (C**8** and C**15**), 132.7 (C**1**), 129.0, 128.3, 128.1 (C**16**, C**17** and C**18**), 124.6 (C**4**), 120.5 (C**3**), 118.5 (C**2**), 114.4 (C**5**), 94.0 (C**7**), 55.6 (C**19**), 49.9 (C**14**), 46.9 (C**10**), 39.0 (C**12**), 27.1 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{21}H_{21}N_2O_3$: 349.1547. Found [M + H] $^+$: 349.1561. *The structure of this compound was determined unambiguously by X-ray crystallography.*



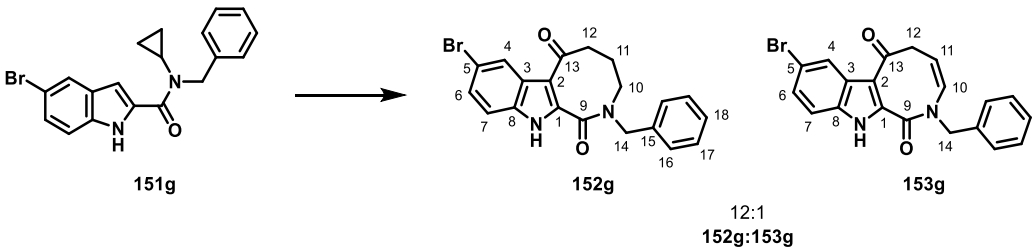
Data for minor compound **153f**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.70 (1H, td, *J* = 8.5, 7.5 Hz, C**11**-H).

***N*-Benzyl-5-bromo-*N*-cyclopropyl-1*H*-indole-2-carboxamide (151g)**



General Procedure A: 5-Bromo-1*H*-indole-2-carboxylic acid (476 mg, 2.00 mmol) and *N*-benzylcyclopropylamine (308 mg, 2.10 mmol) were employed to afford the title compound **151g** (420 mg, 67%) as a beige solid (420 mg, 57%). The crude material was isolated with good purity and was used without further purification. m.p.: 198–201 °C (ethanol); ν_{max}/ cm^{-1}: 3260 (br. m), 1604 (s), 1518 (m), 1433 (s), 1340 (s), 1293 (s), 1267 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.87 (1H, br. s, NH), 7.81 (1H, d, *J* = 2.0 Hz, C**4**-H), 7.41 (1H, d, *J* = 9.0 Hz, C**7**-H), 7.38 – 7.24 (6H, m, C**6**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.15 (1H, s, C**2**-H), 4.78 (2H, s, C**10**-H_2), 3.06 (1H, m, C**15**-H), 0.90 – 0.66 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.7 (C**9**), 138.3 (C**11**), 134.5 (**C8**), 131.9 (C**1**), 128.9 (C**3**), 128.5, 127.1, 126.9 (C**12**, C**13** and C**14**), 126.0 (C**6**), 123.7 (C**4**), 114.2 (C**7**), 111.9 (C**5**), 105.3 (C**2**), 50.6 (C**10**), 31.0 (C**15**), 10.1 (C**16**); HRMS: (ESI)$^{+}$ Calculated for $C_{19}H_{18}{}^{79}BrN_2O$: 369.0597. Found [M + H]$^{+}$: 369.0610.

2-Benzyl-8-bromo-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153g) and **(*Z*)-2-Benzyl-8-bromo-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153g)**



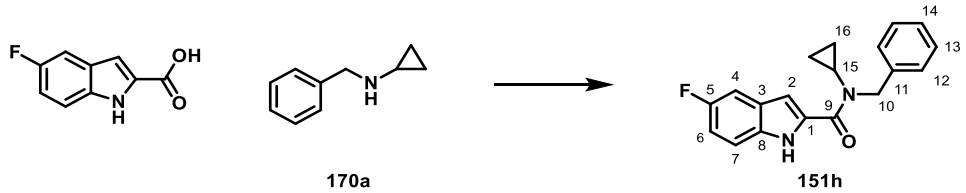
General Procedure C: Indole **151g** (36.7 mg, 0.10 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (20–35% EtOAc/pentane) to yield the title compound **152g** (7.2 mg, 18%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 12:1 (**152g**:**153g**) mixture of products. The minor product **153g** was not isolated.

Data for major compound **152g**: ν_{max}/ cm^{-1}: 3220 (br. m), 2930 (m), 1610 (br. s), 1583 (s), 1520 (s), 1452 (s), 1420 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.77 (1H, br. s, NH), 8.67 (1H, m, C**4**-H), 7.43 (1H, dd, *J* = 8.5, 2.0 Hz, C**6**-H), 7.38 – 7.34 (5H, m, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.29 (1H, dd, *J* =

8.5, 0.5 Hz, C**7**-H), 4.87 (2H, s, C**14**-H$_2$), 3.67 (2H, br. m, C**10**-H$_2$), 2.83 (2H, br. m, C**12**-H$_2$), 2.00 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.9 (C**13**), 163.9 (C**9**), 136.4 (C**15**), 134.6 (C**1**), 133.6 (C**8**), 129.1 128.8, 128.4, 128.3 (C**6**, C**16**, C**17** and C**18**), 127.7 (C**3**), 126.4 (C**4**), 117.6, 117.3 (C**2** and C**5**), 113.1 (C**7**), 49.8 (C**14**), 46.7 (C**10**), 38.9 (C**12**), 26.8 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{18}{}^{79}BrN_2O_2$: 397.0546. Found [M + H] $^+$: 397.0529.

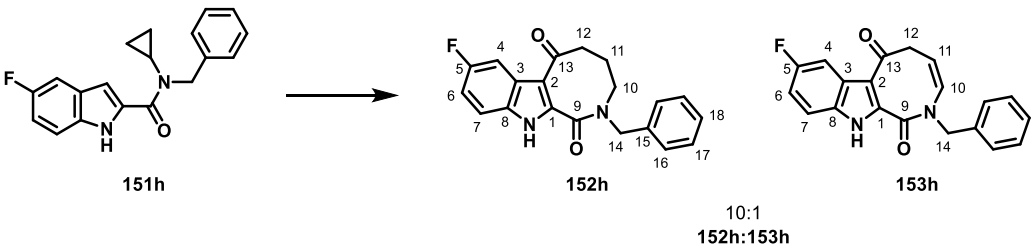
Data for minor compound **153g**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.79 (1H, m, C**11**-H).

***N*-Benzyl-*N*-cyclopropyl-5-fluoro-1*H*-indole-2-carboxamide (151h)**



General Procedure A: 5-Fluoro-1*H*-indole-2-carboxylic acid (358 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed. The crude residue was recrystallised from ethanol to afford the title compound **151h** (470 mg, 76%) as an off-white solid; m.p.: 216–219 °C (ethanol); ν_{max}/ cm^{-1}: 3258 (m), 1602 (s), 1524 (s), 1435 (s), 1404 (s), 1274 (s), 1162 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (1H, br. s, NH), 7.40 – 7.25 (6H, m, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.20 – 7.11 (1H, br. s, C**2**-H), 7.06 (1H, dd, *J* = 9.0, 2.5 Hz, C**6**-H), 4.91 (2H, s, C**10**-H$_2$), 3.03 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 1.03 – 0.84 (4H, m, 2 × C**16**-H$_2$); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.8 (C**9**), 157.03 (d, *J* = 232.5 Hz, C**5**), 138.4 (C**11**), 132.6, 132.3 (C**1** and C**8**), 128.5 (C**13**), 127.2 (C**3**), 127.1 (C**12**), 126.9 (C**14**), 113.34 (d, *J* = 9.6 Hz, C**7**), 112.2 (d, *J* = 26.4 Hz, C**6**), 105.9 (C**2**), 105.7 (d, *J* = 22.9 Hz, C**4**), 50.6 (C**10**), 38.9 (C**15**), 31.0 (C**16**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -123.52 (s); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{18}FN_2NaO$: 331.1217. Found [M + Na] $^+$: 331.1224.

2-Benzyl-8-fluoro-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (152h) and **(*Z*)-2-Benzyl-8-fluoro-2,5-dihydro-1H-azocino[3,4-*b*]indole-1,6(11*H*)-dione (153h)**



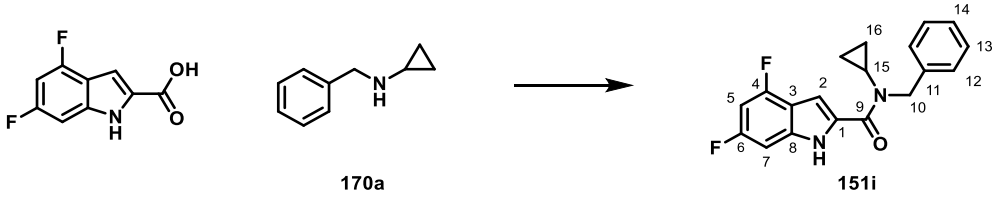
General Procedure C: Indole **151h** (46.2 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (10–15% EtOAc/toluene) to yield the title compound **152h** (34.9 mg, 65%) as an orange solid. Analysis of the

crude reaction mixture by ^{1}H NMR revealed a 10:1 (**152h**:**153h**) mixture of products. The minor product **153h** was not isolated.

Data for major compound **153h**: m.p.: 216–220 °C (CH_2Cl_2/hexane); ν_{max}/ cm^{-1}: 3223 (br. m), 3031 (m), 1613 (br. s), 1518 (m), 1492 (m), 1451 (s), 1424 (s), 1258 (m), 1156 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (1H, br. s, NH), 8.16 (1H, dd, *J* = 10.0, 2.5 Hz, C**4**-H), 7.39 – 7.27 (6H, m, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.05 (1H, dd, *J* = 9.0, 2.5 Hz, C**6**-H), 4.90 (2H, s, C**14**-H_2), 3.69 (2H, br. m, C**10**-H_2), 2.85 (2H, br. m, C**12**-H_2), 2.01 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.8 (C**13**), 164.4 (C**9**), 160.19 (d, *J* = 239.0 Hz, C**5**), 136.3 (C**15**), 135.0 (C**1**), 132.0 (C**8**), 129.1, 128.2, (2 signals) (C**16**, C**17** and C**18**), 126.8 (d, *J* = 11.5 Hz, C**3**), 118.3 (d, *J* = 5.2 Hz, C**2**), 114.4 (d, *J* = 26.9 Hz, C**6**), 113.0 (d, *J* = 9.7 Hz, C**7**), 108.6 (d, *J* = 25.3 Hz, C**4**), 49.9 (C**14**), 46.9 (C**10**), 38.8 (C**12**), 26.8 (C**11**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -119.06 (s); HRMS: (ESI)$^{+}$ Calculated for $C_{20}H_{17}FN_2NaO_2$: 359.1166. Found [M + H] $^{+}$: 359.1149.

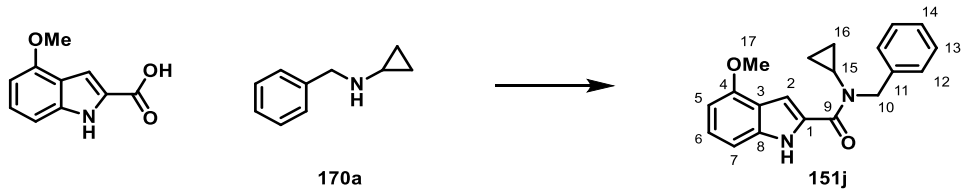
Data for minor compound **153h**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.05 (1H, d, *J* = 7.5 Hz, C**10**-H), 5.75 (1H, m, C**11**-H).

***N*-Benzyl-*N*-cyclopropyl-4,6-difluoro-1*H*-indole-2-carboxamide (151i)**



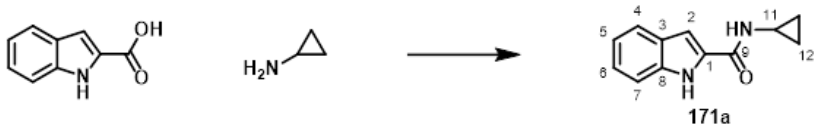
General Procedure A: 4,6-Difluoro-1*H*-indole-2-carboxylic acid (397 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed. The crude residue was recrystallised from ethanol to afford the title compound **151i** as a beige solid (370 mg, 57%); m.p.: 204–205 °C (ethanol); ν_{max}/ cm^{-1}: 3263 (br. m), 1644 (s), 1602 (s), 1581 (s), 1520 (s), 1435 (s), 1290 (s), 1151 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.23 (1H, br. s, NH), 7.40 – 7.27 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.21 (1H, br. s, C**2**-H), 6.82 (1H, dd, *J* = 9.0, 2.0 Hz, C**5**-H), 6.60 (1H, ddd, *J* = 10.0, 2.5, 2.0 Hz, C**7**-H), 4.91 (2H, s, C**10**-H_2), 3.04 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 1.03 – 0.84 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.1 (C**9**), 160.79 (dd, *J* = 242.5, 11.7 Hz, C**6**), 156.79 (dd, *J* = 251.8, 15.2 Hz, C**4**), 137.7 (C**11**), 136.98 (dd, *J* = 15.2, 12.4 Hz, C**8**), 130.5 (d, *J* = 3.5 Hz, C**1**), 128.7, 127.4 (2 signals) (C**12**, C**13** and C**14**), 114.2 (d, *J* = 21.8 Hz, C**3**), 103.2 (C**2**), 95.9 (dd, *J* = 29.4, 22.9 Hz, C**5**), 94.0 (dd, *J* = 26.2, 4.7 Hz, C**7**), 51.9 (C**10**), 31.4 (C**15**), 10.9 (C**16**); ^{19}F NMR (283 MHz, $CDCl_3$): δ -114.2 (dd, *J* = 9.0, 5.7 Hz), -117.5 (ddd, *J* = 10.0, 5.7, 2.5 Hz); HRMS: (ESI)$^{+}$ Calculated for $C_{19}H_{17}F_2N_2O$: 327.1303. Found [M + H] $^{+}$: 327.1318.

***N*-Benzyl-*N*-cyclopropyl-4-methoxy-1*H*-indole-2-carboxamide (151j)**



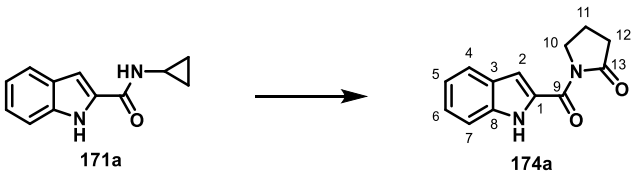
General Procedure A: 4-Methoxy-1H-indole-2-carboxylic acid (382 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed. The crude residue was recrystallised from ethanol to afford the title compound **151j** as a yellow solid (384 mg, 60%); m.p.: 197–198 °C (ethanol); ν_{max}/ cm^{-1}: 3274 (br. m), 1591 (s), 1576 (s), 1513 (s), 1419 (s), 1362 (s), 1249 (s), 1098 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.57 (1H, br. s, NH), 7.38 – 7.23 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.15 (1H, s, C**2**-H), 7.12 (1H, dd, *J* = 8.0, 7.5 Hz, C**6**-H), 7.05 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H), 6.51 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 4.78 (2H, s, C**10**-H_2), 3.87 (3H, s, C**17**-H_3), 3.11 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 0.85 – 0.80 (2H, m, 1 × C**16**-H_2), 0.72 – 0.66 (2H, m, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.9 (C**9**), 153.7 (C**4**), 138.5 (C**11**), 137.3 (C**8**), 129.2 (C**1**), 128.5, 127.0 (C**12**, C**13**), 126.9 (C**14**), 124.6 (C**6**), 118.1 (C**3**), 105.3 (C**7**), 103.2 (C**2**), 99.0 (C**5**), 55.0 (C**17**), 50.6 (C**10**), 31.0 (C**15**), 10.2 (C**16**); HRMS: $(ESI)^+$ Calculated for $C_{20}H_{21}N_2O_2$: 321.1598. Found $[M + H]^+$: 321.1595.

***N*-Cyclopropyl-1*H*-indole-2-carboxamide (171a)**



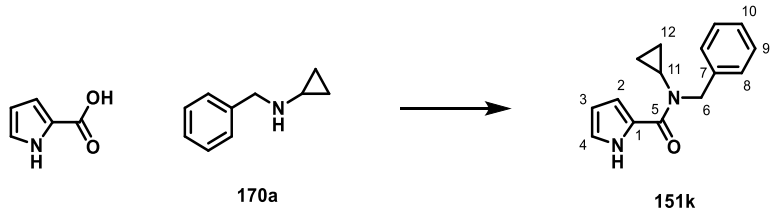
General Procedure A: 1*H*-indole-2-carboxylic acid (322 mg, 2.00 mmol) and cyclopropanamine (116 mg, 2.10 mmol) were employed. The crude residue was recrystallised from ethanol to afford the title compound **171a** as an off-white solid (220 mg, 55%); m.p.: 188–189 °C (ethanol); ν_{max}/ cm^{-1}: 3310 (m), 3283 (m), 2923 (m), 1621 (s), 1538 (s), 1502 (s), 1309 (s), 1263 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (1H, br. s, NH), 7.64 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.45 (1H, d, *J* = 8.5 Hz, C**7**-H), 7.28 (1H, m, C**6**-H), 7.14 (1H, dd, *J* = 8.0, 7.5 Hz, C**5**-H), 6.78 (1H, s, C**2**-H), 6.31 (1H, br. s, NH), 2.93 (1H, m, C**10**-H), 0.80 (4H, br. m, 2 × C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.2 (C**9**), 136.5 (C**8**), 130.7 (C**1**), 127.8 (C**3**), 124.7 (C**6**), 122.0 (C**4**), 120.8 (C**5**), 112.2 (C**7**), 102.1 (C**2**), 23.0 (C**10**), 7.1 (C**11**); HRMS: $(ESI)^+$ Calculated for $C_{12}H_{13}N_2O$: 201.1022. Found $[M + H]^+$: 201.1029.

1-(1*H*-Indole-2-carbonyl)pyrrolidin-2-one (174a)



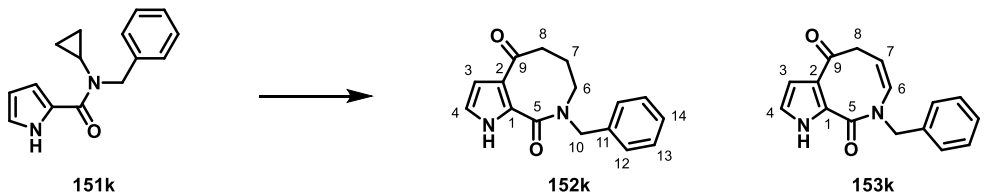
General Procedure C: *In a modification to General procedure C, [Rh(cod)$_2$]OTf (7.5 mol%) was used instead of [Rh(cod)OMe]$_2$ (3.75 mol%) and the reagents were dissolved in argon sparged anhydrous PhCN (0.10 M).* Indole **171a** (20.0 mg, 0.10 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (10–35% EtOAc/pentane) to yield the title compound **174a** (11.4 mg, 50%) as a colourless oil. ν_{max}/ cm^{-1}: 3268 (br. m), 3064 (m), 2926 (m), 1716 (s), 1679 (s), 1527 (s), 1470 (s), 1348 (s), 1237 (s), 1128 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.8 (1H, br. s, NH), 7.70 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.59 (1H, s, C**2**-H), 7.44 (1H, m, C**7**-H), 7.33 (1H, ddd, *J* = 8.5, 7.0, 1.0 Hz, C**6**-H), 7.14 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-H), 4.11 – 4.03 (2H, m, C**10**-H$_2$), 2.77 (2H, t, *J* = 8.0 Hz, C**12**-H$_2$), 2.27 – 2.10 (2H, m, C**11**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5 (C**13**), 161.3 (C**9**), 137.2 (C**8**), 129.3 (C**1**), 127.2 (C**3**), 126.1 (C**6**), 122.9 (C**4**), 120.9 (C**5**), 113.7 (C**2**), 112.6 (C**7**), 48.2 (C**10**), 34.4 (C**12**), 18.1 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{13}H_{12}N_2NaO_2$: 251.0791. Found [M + Na]$^+$: 251.0796.

***N*-Benzyl-*N*-cyclopropyl-1*H*-pyrrole-2-carboxamide (151k)**



General Procedure B: 1*H*-Pyrrole-2-carboxylic acid (1.10 g, 10.0 mmol) and *N*-benzylcyclopropylamine **170a** (1.54 g, 10.5 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (10% EtOAc/CH_2Cl_2) to give the title compound **151k** (1.80 g, 75%) as a colourless solid; m.p.: 141–143 °C (ethanol); ν_{max}/ cm^{-1}: 3175 (br. m), 2945 (m), 1576 (s), 1440 (m), 1422 (s), 1139 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (1H, br. s, NH), 7.34 – 7.21 (5H, m, 2 × C**8**-H, 2 × C**9**-H and C**10**-H), 6.94 (1H, dd, *J* = 2.5, 1.5 Hz, C**4**-H), 6.88 (1H, br. m, C**2**-H), 6.27 (1H, dd, *J* = 4.0, 2.5 Hz, C**3**-H), 4.82 (2H, s, C**6**-H$_2$), 2.90 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-H), 0.95 – 0.80 (4H, m, 2 × C**12**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 164.1 (C**5**), 138.5 (C**7**), 128.6, 127.5 (C**8** and C**9**), 127.1 (C**10**), 125.6 (C**1**), 121.5 (C**4**), 114.1 (C**2**), 109.8 (C**3**), 51.5 (C**6**), 31.2 (C**11**), 10.7 (C**12**); HRMS: (ESI)$^+$ Calculated for $C_{15}H_{17}N_2O$: 241.1335. Found [M + H]$^+$: 241.1349.

8-Benzyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*c*]azocine-4,9-dione (152k) and **(*Z*)-8-Benzyl-5,8-dihydro-1*H*-pyrrolo[2,3-*c*]azocine-4,9-dione (153k)**

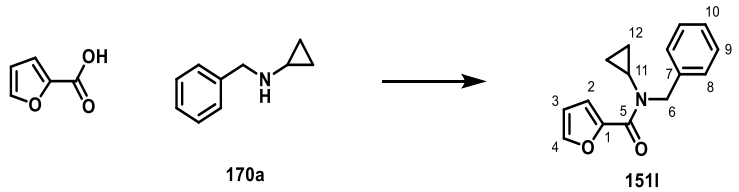


General Procedure C: *In a modification to General procedure C, P(3,4,5-(F)$_3$C$_6$H$_2$)$_3$ (22.5 mol%) was used instead of P(4-(F)C$_6$H$_4$) (22.5 mol%).* Pyrrole **151k** (38.0 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The residue was purified by flash column chromatography (70/20/10%, toluene/EtOAc/CH_2Cl_2) to afford the title compound **152k** (27.8 mg, 69%) as an off white solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 8:1 (**152k**:**153k**) mixture of products. The minor product **153k** was not isolated.

Data for major compound **152k**: m.p.: 145–148°C (CH_2Cl_2/hexane); ν_{max}/ cm^{-1}: 3217 (br. m), 3029 (m), 1652 (m), 1601 (s), 1469 (s), 1434 (m), 1137 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.4 (1H, br. s, N<u>H</u>), 7.35 – 7.27 (5H, m, 2 × C**12**-<u>H</u>, 2 × C**13**-<u>H</u> and C**14**-<u>H</u>), 6.81 (1H, d, *J* = 3.0 Hz, C**3**-<u>H</u>), 6.71 (1H, d, *J* = 3.0 Hz, C**4**-<u>H</u>), 4.82 (2H, s, C**10**-<u>H$_2$</u>), 3.60 (2H, t, *J* = 6.0 Hz, C**6**-<u>H$_2$</u>), 2.76 (2H, t, *J* = 6.0 Hz, C**8**-<u>H$_2$</u>), 1.94 (2H, tt, *J* = 6.0, 6.0 Hz, C**7**-<u>H$_2$</u>); ^{13}C NMR (126 MHz, $CDCl_3$): δ 196.1 (C**9**), 164.0 (C**5**), 137.0 (C**11**) 129.0, 128.3 (C**12** and C**13**), 128.0 (C**14**), 127.6, 127.4 (C**1** and C**2**), 121.0 (C**4**), 110.6 (C**3**), 49.9 (C**10**), 46.8 (C**6**), 38.6 (C**8**), 27.1 (C**7**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{16}N_2NaO_2$: 291.1104. Found [M + Na]$^+$: 291.1114.

Data for minor compound **153k**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07 (1H, d, *J* = 7.5 Hz, C**6**-<u>H</u>), 5.63 (1H, m, C**7**-<u>H</u>).

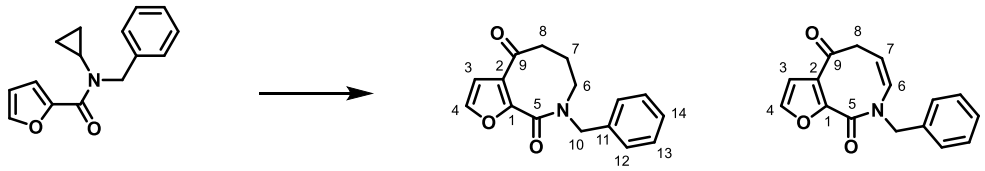
***N*-Benzyl-*N*-cyclopropylfuran-2-carboxamide (151l)**



General Procedure B: Furan-2-carboxylic acid (488 mg, 4.00 mmol) and *N*-benzylcyclopropylamine **170a** (618 mg, 4.20 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to give the title compound **151l** (610 mg, 63 %) as a colourless oil; ν_{max}/ cm^{-1}: 3009 (m), 1626 (s), 1475 (m), 1401 (s), 1370 (m) 1029 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, dd, *J* = 2.0, 1.0 Hz, C**4**-<u>H</u>), 7.40

– 7.20 (5H, m, 2 × C**8**-H, 2 × C**9**-H and C**10**-H), 7.06 (1H, dd, *J* = 3.5, 1.0, C**2**-H), 6.48 (1H, dd, *J* = 3.5, 2.0 Hz, C**3**-H), 4.77 (2H, s, C**6**-H_2), 2.87 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-H), 0.82 – 0.62 (4H, m, 2 × C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.1 (C**5**), 148.4 (C**1**), 144.2 (C**4**), 138.0 (C**7**), 128.7, 128.0, 127.4 (C**8**, C**9** and C**10**), 116.3 (C**2**), 111.3 (C**3**), 51.3 (C**6**), 31.0 (C**11**), 9.6 (C**12**); HRMS: (ESI)$^+$ Calculated for $C_{15}H_{15}NNaO_2$: 264.0995. Found [M + Na] $^+$: 264.1007.

8-Benzyl-5,6,7,8-tetrahydrofuro[2,3-*c*]azocine-4,9-dione (152l) and **(*Z*)-8-Benzyl-5,8-dihydrofuro[2,3-*c*]azocine-4,9-dione (153l)**

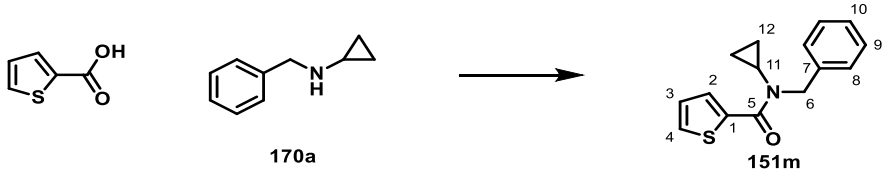


General Procedure C: Furan **151l** (38.0 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The residue was purified by flash column chromatography (10–30% EtOAc/petroleum ether) to afford the title compound **152l** (24.9 mg, 62%) as a yellow oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 6:1 (**152l**:**153l**) mixture of products. The minor product **153l** was not isolated.

Data for major compound **152l**: ν_{max}/ cm^{-1}: 2923 (m), 2854 (m), 1673 (s), 1642 (s), 1501 (m), 1401 (m), 1176 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, *J* = 2.0 Hz, C**4**-H), 7.39 – 7.29 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.84 (1H, d, *J* = 2.0 Hz, C**3**-H), 4.81 (2H, s, C**10**-H_2), 3.54 (2H, t, *J* = 6.5 Hz, C**6**-H_2), 2.84 – 2.66 (2H, m, C**8**-H_2), 1.93 (2H, tt, *J* = 6.5, 6.5 Hz, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.3 (C**9**), 161.1 (C**5**), 148.2 (C**1**), 144.7 (C**4**), 136.6 (C**11**), 129.0, 128.9, 128.7 (C**2**, C**12** and C**13**), 128.2 (C**14**), 109.9 (C**3**), 49.1 (C**10**), 46.0 (C**6**), 38.3 (C**8**), 26.4 (C**7**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{16}N_2O_3$: 270.1125. Found [M + H] $^+$: 270.1125.

Data for the minor product **153l**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.05 (1H, dd, *J* = 7.5, 1.0 Hz, C**6**-H), 5.57 (1H, m, C**7**-H).

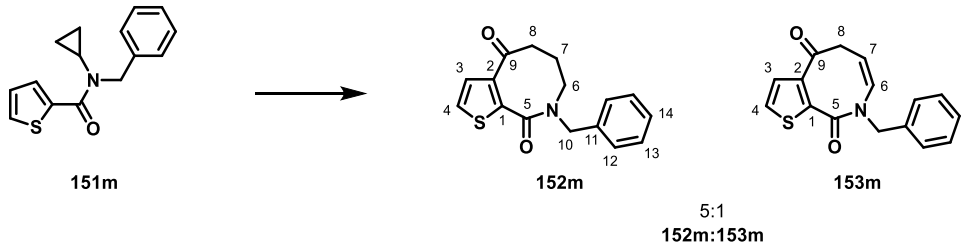
***N*-Benzyl-*N*-cyclopropylthiophene-2-carboxamide (151m)**



General Procedure B: Thiophene-2-carboxylic acid (254 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (309 mg, 2.10 mmol) were employed and the reaction was stirred at

room temperature for 18 hours to afford the title compound **151m** (324 mg, 63 %) as a colourless oil. The crude material was used without further purification. ν_{max}/ cm^{-1}: 3005 (m), 1609 (s), 1423 (s), 1395 (s), 1369 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, dd, *J* = 4.0, 1.0 Hz, ArC-H), 7.42 (1H, dd, *J* = 5.0, 1.0 Hz, ArC-H), 7.30 – 7.18 (5H, m, 2 × C**8**-H, 2 × C**9**-H and C**10**-H), 6.99 (1H, dd, *J* = 5.0, 4.0 Hz, C**3**-H), 4.73 (2H, s, C**6**-H_2), 2.78 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-H), 0.79 – 0.64 (4H, m, 2 × C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5 (C**5**), 138.9 (C**1**), 138.0 (C**7**), 130.8 (Ar-CH), 129.9 (Ar-CH), 128.7, 127.5, 127.4 (C**8**, C**9** and C**10**) 126.9 (C**3**) 51.9 (C**6**), 31.5 (C**11**), 11.0 (C**12**); HRMS: $(ESI)^+$ Calculated for $C_{15}H_{15}NNaOS$: 280.0767. Found $[M + Na]^+$: 280.0758.

8-Benzyl-5,6,7,8-tetrahydrothieno[2,3-*c*]azocine-4,9-dione (152m) and **(*Z*)-8-Benzyl-5,8-dihydrothieno[2,3-*c*]azocine-4,9-dione (153m)**



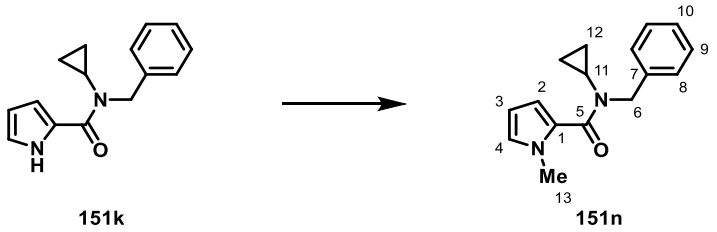
General Procedure C: Thiophene **151m** (38.0 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The residue was purified by flash column chromatography (10–30% EtOAc/pentane) to yield the title compound **152m** (21.4 mg, 50%) as a yellow oil and minor product **153m** (4.4 mg, 10%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 5:1 (**152m**:**153m**) mixture of products.

Data for major compound **152m**: ν_{max}/ cm^{-1}: 2927 (m), 1667 (s), 1614 (s), 1513 (m), 1440 (s), 1257 (m), 1221 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, *J* = 5.5 Hz, ArC-H), 7.40 – 7.28 (6H, m, ArC-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 4.82 (2H, s, C**10**-H_2), 3.51 (2H, br. m, C**6**-H_2), 2.77 (2H, br. m, C**8**-H_2), 1.92 (2H, tt, *J* = 6.5, 6.5 Hz, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): 194.6 (C**9**), 164.2 (C**5**), 143.8 (Ar-C), 141.0 (Ar-C), 136.8 (C**11**), 129.0, 128.5 (C**12** and C**13**), 128.4, 128.1, 127.9 (C**3**, C**4** and C**14**), 49.5 (C**10**), 46.2 (C**6**), 37.5 (C**8**), 26.6 (C**7**); HRMS: $(ESI)^+$ Calculated for $C_{16}H_{15}NNaO_2S$: 308.0716. Found $[M + Na]^+$: 308.0707.

Data for the minor product **153m**: ν_{max}/ cm^{-1}: 2926 (m), 1682 (s), 1616 (s), 1514 (m), 1432 (m), 1339 (m), 1263 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 5.5 Hz, ArC-H), 7.42 – 7.27 (6H, m, ArC-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.17 (1H, d, *J* = 7.5 Hz, C**6**-H), 5.64 (1H, d, *J* = 8.5 Hz, C**7**-H), 5.24 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 4.58 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 3.36 (1H, m, 1H, 1 × C**8**-H_2), 3.06 (1H, m, 1H, 1 × C**8**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.7 (C**9**), 162.5 (C**5**), 143.9 (Ar-C), 136.5 (Ar-C), 136.2 (Ar-C), 131.3 (C**6**), 128.9, 128.7 (C**12** and C**13**), 128.5, 128.2, 127.8 (C**3**, C**4**

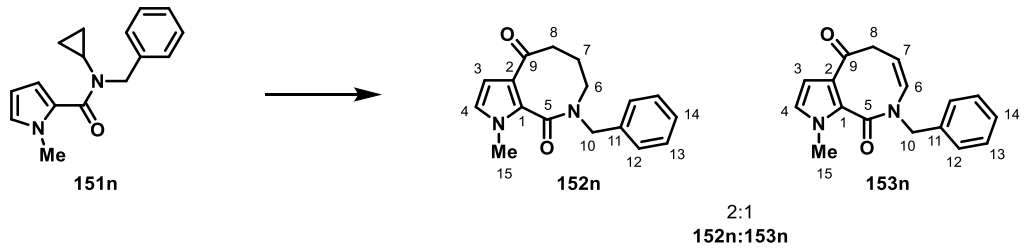
and C**14**), 121.5 (C**7**), 52.1 (C**10**), 41.4 (C**8**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{13}NNaO_2S$: 306.0559. Found [M + Na]$^+$: 306.0553.

***N*-Benzyl-*N*-cyclopropyl-1-methyl-1*H*-pyrrole-2-carboxamide (151n)**



A flame-dried round-bottomed flask was charged with NaH (120 mg, 3.00 mmol, 60% dispersion in mineral oil) and suspended in DMF (8.0 mL) under nitrogen. The suspension was cooled to 0 °C and **151k** (600 mg, 2.50 mmol) was added portion wise over 10 minutes. The solution was stirred at 0 °C for 1 hour, followed by dropwise addition of iodomethane (0.19 mL, 3.00 mmol). The solution was then allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **151n** (600 mg, 95%) as a colourless oil; ν_{max}/ cm^{-1}: 2935 (m), 1617 (s), 1529 (s), 1421 (s), 1388 (s), 1368 (s), 1251 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.22 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 6.70 (1H, dd, *J* = 2.5, 1.5 Hz, C**4**-H), 6.58 (1H, dd, *J* = 4.0, 1.5 Hz, C**2**-H), 6.08 (1H, dd, *J* = 4.0, 2.5Hz, C**3**-H), 4.77 (2H, s, C**6**-H_2), 3.84 (3H, s, C**13**-H_3), 2.72 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-H), 0.79 – 0.57 (4H, m, 2 × C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5 (C**5**), 138.4 (C**7**), 128.9, 127.8 (C**8**, C**9**), 127.3 (C**10**), 126.8 (C**4**), 126.3 (C**1**), 114.4 (C**2**), 106.9 (C**3**), 51.7 (C**6**), 36.4 (C**13**), 31.3 (C**11**), 10.1 (C**12**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{19}N_2O$: 255.1491. Found [M + H]$^+$: 255.1504.

8-Benzyl-1-methyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[2,3-*c*]azocine-4,9-dione (152n) and **(*Z*)-8-Benzyl-1-methyl-5,8-dihydro-1*H*-pyrrolo[2,3-*c*]azocine-4,9-dione (153n).**



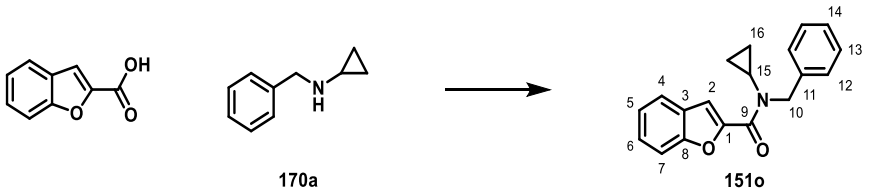
General Procedure C: *In a modification to General procedure C, [Rh(cod)$_2$]OTf (7.5 mol%) was used instead of [Rh(cod)OMe]$_2$ (3.75 mol%) and the reagents were dissolved in argon sparged anhydrous PhCN (0.10 M).* Pyrrole **151n** (38.6 mg, 0.15 mmol) was employed and the reaction mixture was heated

at 140 °C for 72 h. The residue was purified by flash column chromatography (20–40% EtOAc/petroleum ether) to yield the title compound **152m** (20.0 mg, 48%) as a colourless oil and **153n** (10.0 mg, 24%) as a colourless oil.

Data for major compound **152n**: ν_{max}/ cm^{-1}: 2924 (m), 1645 (s), 1626 (s), 1490 (s), 1470 (s), 1443 (s), 1216 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (4H, m, 2 × C**12**-H and 2 × C**13**-H), 7.30 (1H, m, C**14**-H), 6.69 – 6.65 (2H, m, C**3**-H and C**4**-H), 5.31 (1H, br. m, 1 × C**10**-H_2), 4.30 (1H, br. m, 1 × C**10**-H_2), 3.80 (4H, br. m, 1 × C**6**-H_2 and C**15**-H_3), 3.28 (1H, br. m, 1 × C**6**-H_2), 2.68 (2H, br. m, C**8**-H_2), 1.91 (2H, br. m, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 194.5 (C**9**), 163.5 (C**5**), 137.1 (C**11**), 128.9, 128.6, 128.2, 128.1 (C**1**, C**2**, C**12** and C**13**), 127.9 (C**14**), 126.5 (C**4**), 108.6 (C**3**), 48.2 (C**10**), 45.9 (C**6**), 37.5 (C**8**), 36.7 (C**15**), 26.0 (C**7**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{19}N_2O_2$: 283.1441. Found $[M + H]^+$: 283.1450.

Data for minor compound **153n**: ν_{max}/ cm^{-1}: 2925 (m), 1667 (s), 1621 (s), 1488 (s), 1442 (s), 1428 (s), 1243 (s), 1105 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.28 (5H, m, 2 × C**12**-H and 2 × C**13**-H and C**14**-H), 6.67 (1H, d, *J* = 3.0 Hz, C**4**-H), 6.60 (2H, d, *J* = 3.0 Hz, C**3**-H), 6.10 (1H, dd, *J* = 7.5, 1.0 Hz, C**6**-H), 5.70 (1H, ddd, *J* = 10.5, 7.5, 7.0 Hz, C**7**-H), 5.10 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 4.69 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 3.72 (3H, s, C**15**-H_3), 3.23 (1H, ddd, *J* = 12.5, 10.5, 1.0 Hz, 1 × C**8**-H_2), 2.94 (1H, dd, *J* = 12.5, 7.0 Hz, 1 × C**8**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.4 (C**9**), 161.6 (C**5**), 136.4 (C**11**), 130.1 (C**6**), 129.1 (C**1**), 128.9, 128.7, 128.2 (C**12**, C**13** and C**14**), 126.5 (**C4**), 124.0 (C**7**), 123.1 (C**2**), 108.3 (C**3**), 51.2 (C**10**), 41.4 (C**8**), 36.7 (C**15**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{17}N_2O_2$: 281.1285. Found $[M + H]^+$: 281.1281.

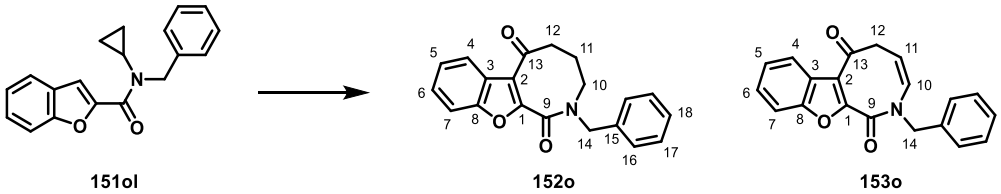
***N*-Benzyl-*N*-cyclopropylbenzofuran-2-carboxamide (151o)**



General Procedure B: Benzofuran-2-carboxylic acid (325 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (309 mg, 2.10 mmol) were employed and the reaction was stirred at r.t. for 18 hours. The crude residue was purified by flash column chromatography (15% EtOAc/petroleum ether) to give the title compound **151o** (500 mg, 86%) as a colourless solid; m.p.: 69–71 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 3029 (m), 1624 (s), 1557 (s), 1434 (m), 1410 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, m, C**4**-H), 7.52 (1H, m, C**7**-H), 7.40 (1H, dd, *J* = 7.0, 1.5 Hz, C**6**-H), 7.38 – 7.24 (7H, m, C**2**-H, C**5**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 4.83 (2H, s, C**10**-H_2), 2.97 (1H, m, C**15**-H), 0.83 – 0.65 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7 (C**9**), 154.8 (C**8**), 149.5 (C**1**), 137.6 (C**11**), 128.6, 128.0, 127.4 (C**12**, C**13** and C**14**) 127.1 (C**3**), 126.4 (C**6**), 123.4 (C**5**), 122.3 (C**4**),

111.9, 111.8 (C**2** and C**7**), 51.3 (C**10**), 31.0 (C**15**), 9.4 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{18}NO_2$: 292.1332. Found [M + H] $^+$: 292.1339.

2-Benzyl-2,3,4,5-tetrahydrobenzofuro[2,3-*c*]azocine-1,6-dione (152o) and **(*Z*)-2-Benzyl-2,5-dihydrobenzofuro[2,3-*c*]azocine-1,6-dione (153o)**

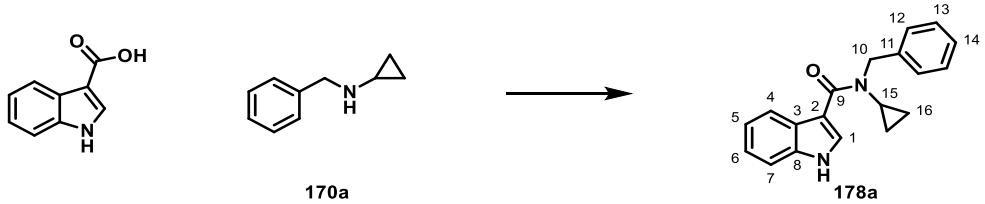


General Procedure C: *In a modification to general procedure C, [Rh(cod)$_2$]OTf (7.5 mol%) was used instead of [Rh(cod)OMe]$_2$ (3.75 mol%) and the reagents were dissolved in argon sparged anhydrous PhCN (0.10 M).* Benzofuran **151o** (29.0 mg, 0.10 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The conversion to products **152o**/**153o** was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. This revealed 24% **152o** and 8% **153o**. An analytical sample of **152o** was also isolated for characterisation by flash column chromatography (5–30% EtOAc/pentane). The minor product **153o** was not isolated.

Data for major compound **152o**: ν_{max}/ cm^{-1}: 2926 (m), 1638 (s), 1551 (s), 1468 (m), 1439 (m), 1141 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (1H, dd, *J* = 7.5, 1.5 Hz, C**4**-H), 7.54 – 7.31 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 4.87 (2H, br. s, C**14**-H$_2$), 3.62 (2H, br. m, C**10**-H$_2$), 2.84 (2H, br. m, C**12**-H$_2$), 1.99 (2H, tt, *J* = 6.5, 6.5 Hz, C**11**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 195.5 (C**13**) 161.6 (C**9**), 154.5 (C**8**), 150.8 (C**1**), 136.5 (C**15**), 129.08, 129.0, 128.7, 128.1 (C**3**, C**16**, C**17** and C**18**), 127.5 (C**6**), 125.4 (C**5**), 124.5 (C**4**), 122.2 (C**2**), 111.9 (C**7**), 49.1 (C**14**), 45.9 (C**10**), 38.8 (C**12**), 26.3 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{17}NNaO_3$: 342.1101. Found [M + Na] $^+$: 342.1108.

Data for the minor product **153o**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR 6.17 (1H, dt, *J* = 7.5, 1.0 Hz, C10-H), 5.76 (1H, m, C11-H).

***N*-Benzyl-*N*-cyclopropyl-1*H*-indole-3-carboxamide (178a)**



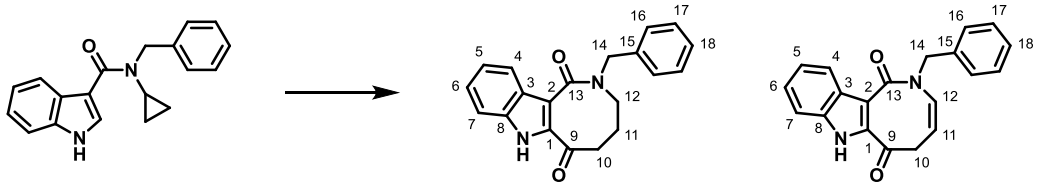
General Procedure A: 1*H*-Indole-3-carboxylic acid (500 mg, 3.10 mmol) and *N*-benzylcyclopropylamine **170a** (480 mg, 3.26 mmol) were employed and the reaction was stirred at

room temperature for 4 hours. The crude residue was recrystallised from EtOH to give the title compound **178a** (715 mg, 79%) as a white crystalline solid.

General Procedure A: *(Multi-mmol scale reaction for material throughput).* 1*H*-Indole-3-carboxylic acid (6.00g, 37.2 mmol) and *N*-benzylcyclopropylamine **170a** (5.76 g, 39.1 mmol) were employed and the reaction was stirred at room temperature for 4 hours. The crude residue was recrystallised from MeOH to give the title compound **178a** (8.01 g, 75%) as a white crystalline solid.

Data for compound **178a**: m.p.: 143–145 °C (EtOH); ν_{max}/ cm^{-1}: 3271 (br. m), 2982 (m), 1616 (s), 1521 (m), 1401 (s), 1313 (m), 1280 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (1H, br. s, NH), 8.01 (1H, dd, *J* = 6.5, 3.0 Hz, C**4**-H), 7.40 – 7.22 (7H, m, C**1**-H, C**7**-H 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.20 – 7.14 (2H, m, C**5**-H and C**6**-H), 4.83 (2H, s, C**10**-H_2), 2.69 (1H, tt, *J* = 6.5, 4.5 Hz, C**15**-H), 0.71 – 0.63 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3 (C**9**), 138.5 (C**11**), 135.8 (C**3**), 128.7, 128.0, 127.9 (C**1,** C**12** and C**13**), 127.3 (C**14**), 126.7 (C**8**), 122.7 (C**5**), 121.2 (C**4**), 121.1 (C**6**), 111.8 (C**2**), 111.2 (C**7**), 51.7 (C**10**), 31.0 (C**15**), 10.3 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{19}N_2O$: 291.1491. Found [M + H]$^+$: 291.1502.

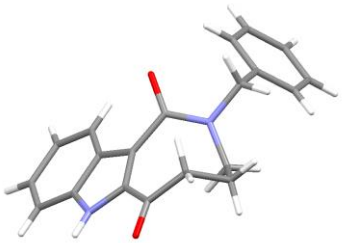
2-Benzyl-2,3,4,5-tetrahydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (179a) and **(*Z*)-2-Benzyl-2,5-dihydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (180a)**



General Procedure C: Indole **178a** (43.5 mg, 0.15 mmol) was employed and the reaction mixture was heated at 130 °C for 72 h. The residue was purified by flash column chromatography (5–10% acetone/toluene) to yield the title compound **179a** (27.7 mg, 58%) as a yellow solid and **180a** (2.4 mg, 5%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 10:1 (**179a**: **180a**) mixture of products.

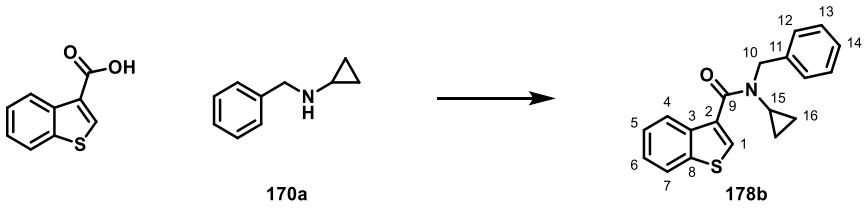
Data for major compound **179a**: m.p. 209–210 °C (EtOAc/petroleum ether); ν_{max}/ cm^{-1}: 3299 (br. m), 2925 (m), 1656 (s), 1605 (s), 1571 (m), 1518 (s), 1466 (s), 1452 (s), 1417 (s), 1331 (s), 1221 (m), 1147 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (1H, br. s, NH), 8.12 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.48 – 7.21 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 5.31 (1H, m, 1 × C**14**-H_2), 4.53 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.82 (1H, m, 1 × C**12**-H_2), 3.32 (1H, m, 1 × C**12**-H_2), 3.14 (1H, m, 1 × C**10**-H_2), 2.63 (1H, d, *J* = 12.5 Hz, 1 × C**10**-H_2), 2.07 (1H, d, *J* = 12.0 Hz, 1 × C**11**-H_2), 1.84 (1H, m, 1 × C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.1 (C**9**), 166.3 (C**13**), 137.5 (C**15**), 136.2 (C**8**), 133.5

(C**1**), 128.9, 128.4, 128.3 (C**3**, C**16** and C**17**), 127.9 (C**6**), 127.4 (C**18**), 123.8 (C**4**), 122.4 (C**5**), 115.2 (C**2**), 112.1 (C**7**), 48.6 (C**14**), 45.8 (C**12**), 36.9 (C**10**), 26.5 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{19}N_2O$: 319.1441. Found [M + H] $^+$: 319.1459. *The structure of this compound was determined unambiguously by X-ray cystrallography.*



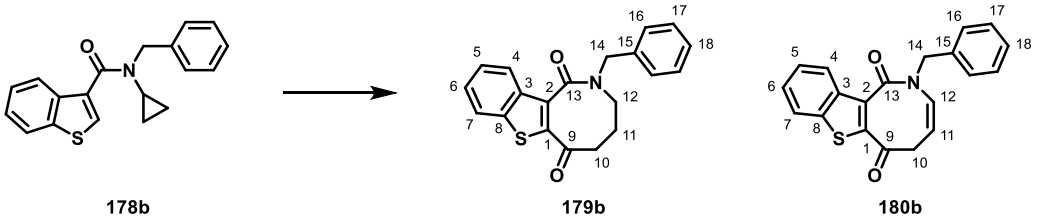
Data for minor compound **180a**: ν_{max}/ cm^{-1}: 3312 (br. m), 2923 (m), 1674 (s), 1612 (s), 1521 (s), 1454 (s), 1386 (m), 1333 (s), 1265 (s), 1228 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (1H, br. s, NH), 8.05 (1H, d, *J* = 8.0, Hz, C**4**-H), 7.51 – 7.23 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 6.16 (1H, dd, *J* = 7.5, 1.0 Hz, C**12**-H), 5.64 (1H, ddd, *J* = 10.0, 7.5, 7.0 Hz, C**11**-H), 5.30 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 4.77 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.53 (1H, ddd, *J* = 12.5, 10.0, 1.0 Hz, 1 × C**10**-H_2), 3.11 (1H, dd, *J* = 12.5, 7.0 Hz, 1 × C**10**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.0 (C**9**), 163.9 (C**13**), 136.8 (C**15**), 135.6 (C**8**), 131.9 (C**12**), 130.6 (C**1**), 128.7, 128.5, 128.4 (C**3**, C**16** and C**17**), 127.8 (C**18**), 126.9 (C**6**), 123.7 (C**4**), 122.3 (C**5**), 120.4 (C**11**), 114.6 (C**2**), 111.8 (C**7**), 51.2 (C**14**), 40.1 (C**10**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{16}N_2NaO$: 339.1104. Found [M + Na] $^+$: 339.1107.

***N*-Benzyl-*N*-cyclopropylbenzo[*b*]thiophene-3-carboxamide (178b)**



General Procedure B: 1-Benzothiophene-3-carboxylic acid (356 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed and the reaction was stirred at room temperature for 6 hours. The crude residue was purified by flash column chromatography (5% EtOAc/ CH_2Cl_2) to give the title compound **178b** (343 mg, 56%) as a colourless oil; ν_{max}/ cm^{-1}: 2982 (m), 1616 (s), 1417 (s), 1280 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.80 (2H, m, 2 × Ar-CH), 7.60 (1H, s, C**2**-H), 7.43 – 7.24 (7H, m, 7 × Ar-CH), 4.77 (2H, s, C**10**-H_2), 2.62 (1H, tt, *J* = 6.5, 4.5 Hz, C**15**-H), 0.62 – 0.50 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C9), 139.6 (ArC), 138.0 (ArC), 137.5 (ArC), 132.7 (ArC), 128.8, 128.2, 127.6, 127.1 (2 signals), 124.9, 123.5, 122.6 (8 × Ar-CH), 51.3 (C**10**), 31.1 (C**15**), 9.4 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{18}NOS$: 308.1103. Found [M + H] $^+$: 308.1103.

2-Benzyl-2,3,4,5-tetrahydrobenzo[4,5]thieno[3,2-*c*]azocine-1,6-dione (179b) and **(*Z*)-2-Benzyl-2,5-dihydrobenzo[4,5]thieno[3,2-*c*]azocine-1,6-dione (180b)**

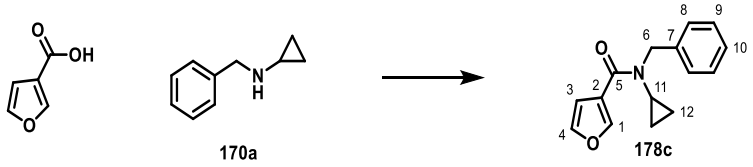


General Procedure C: Benzothiophene **178b** (46.1 mg, 0.15 mmol) was employed and the reaction mixture was heated at 130 °C for 72 h. The conversion to products **179b**/**180b** was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. This revealed 23% **179b** and 4% **180b**. The residue was purified by flash column chromatography (5–10% acetone/toluene); however, the product **179b** could not be readily separated from the ligand, starting material and other side-products. The structure of product **179b** was determined by analysis of the ^{1}H NMR spectrum of partially purified material and corroborated by COSY data and HRMS. The minor product **180b** was not isolated.

Data for the major product **179b**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.18 (1H, d, *J* = 14.0 Hz, 1 × C**14**-$\underline{H}_2$), 4.73 (1H, d, *J* = 14.0 Hz, 1 × C**14**-$\underline{H}_2$), 3.67 (1H, m, 1 × C**12**-$\underline{H}_2$), 3.27 (1H, m, 1 × C**12**-$\underline{H}_2$), 2.65 (1H, m, 1 × C**10**-$\underline{H}_2$); HRMS: (ESI)$^{+}$ Calculated for $C_{20}H_{18}NO_2S$: 336.4210. Found [M + H] $^{+}$: 336.4208.

Data for the minor product **180b**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.17 (d, *J* = 7.5 Hz, C**12**-$\underline{H}$), 5.70 (1H, dt, *J* = 10.0, 7.0 Hz, C**11**-$\underline{H}$).

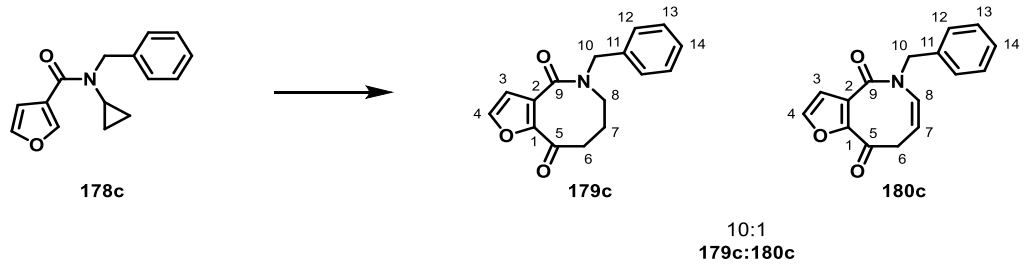
***N*-Benzyl-*N*-cyclopropylfuran-3-carboxamide (178c)**



General Procedure B: Furan-3-carboxylic acid (488 mg, 4.00 mmol) and *N*-benzylcyclopropylamine **170a** (618 mg, 4.20 mmol) were employed to afford the title compound **178c** (690 mg, 72%) as a colourless solid. The crude material was used without further purification. m.p.: 53–55 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 3010 (m), 2940 (m), 1603 (s), 1568 (m), 1414 (s), 1157 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, s, C**1**-$\underline{H}$), 7.40 (1H, d, *J* = 1.5 Hz, C**4**-$\underline{H}$), 7.36 – 7.23 (5H, m, 2 × C**8**-$\underline{H}$, 2 × C**9**-$\underline{H}$, C**10**-$\underline{H}$), 6.78 (1H, m, C**3**-$\underline{H}$), 4.75 (2H, s, C**6**-$\underline{H}_2$), 2.73 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-$\underline{H}$), 0.83 – 0.68 (4H, m, 2 × C**12**-$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1 (C**5**), 145.1 (C**1**), 142.4 (C**4**), 138.2 (C**7**), 128.7, 127.9,

127.4 (C**8**, C**9** and C**10**), 122.5 (C**2**), 111.1 (C**3**), 51.2 (C**6**), 30.9 (C**11**), 10.5 (C**12**); HRMS: (ESI)$^+$ Calculated for $C_{15}H_{15}N_2NaO_2$: 264.0995. Found [M + Na]$^+$: 264.0995.

5-Benzyl-5,6,7,8-tetrahydrofuro[3,2-*c*]azocine-4,9-dione (179c) and **(*Z*)-5-Benzyl-5,8-dihydrofuro[3,2-*c*]azocine-4,9-dione (180c)**

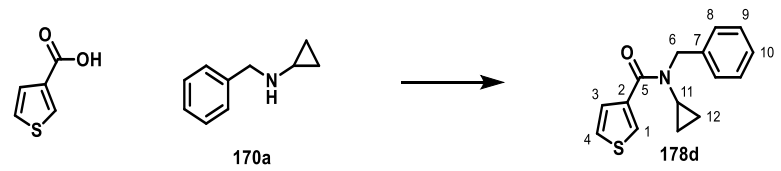


General Procedure C: Furan **178c** (36.2 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The residue was purified by flash column chromatography (15–20% EtOAc/toluene) to yield the title compound **179c** (28.7 mg, 71%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 10:1 (**179c**: **180c**) mixture of products. The minor product **180c** was not isolated.

Data for major compound **179c**: ν_{max}/ cm^{-1}: 2923 (m), 2853 (m), 1672 (s), 1630 (s), 1492 (s), 1394 (s), 1082 (m); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ 7.62 (1H, d, *J* = 2.0 Hz, C**4**-H), 7.41 – 7.25 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.86 (1H, d, *J* = 2.0 Hz, C**3**-H), 4.80 (2H, br. s, C**10**-H_2), 3.48 (2H, br. m, C**8**-H_2), 2.69 (2H, br. m, C**6**-H_2), 1.88 (2H, br. m, C**7**-H_2); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 7.95 (d, *J* = 1.5, C**4**-H), 7.42 – 7.26 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.83 (1H, d, *J* = 1.5 Hz, C**3**-H), 4.74 (2H, s, C**10**-H_2), 3.46 (2H, t, *J* = 6.5 Hz, C**8**-H_2), 2.58 (2H, t, *J* = 6.5 Hz, C**6**-H_2), 1.85 (2H, tt, *J* = 6.5, 6.5 Hz, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$, 20 °C): δ 187.3 (C**5**), 164.5 (C**9**), 149.0 (C**1**), 146.7 (C**4**), 136.9 (C**11**), 129.0, 128.5 (C**12**, C**13**), 128.1 (C**14**), 127.3 (C**2**), 114.6 (C**3**), 49.1 (C**10**), 46.3 (C**8**), 36.8 (C**6**), 26.1 (C**7**); ^{13}C NMR (126 MHz, DMSO-d_6, 100 °C): δ 186.0 (C**5**), 163.2 (C**9**), 148.1 (C**1**), 146.7 (C**4**), 137.1 (C**11**), 128.1, 127.6, 126.7 (C**12**, C**13** and C**14**), 126.5 (C**2**), 113.6 (C**3**), 47.8 (C**10**), 45.6 (C**8**), 36.1 (C**6**), 25.0 (C**7**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{15}NNaO_3$: 292.0944. Found [M + Na] $^+$: 292.0948. *A ^{1}H NMR spectrum was recorded at 100 °C in DMSO-d_6 because at room temperature slow conformational interconversion gave a broad spectrum.*

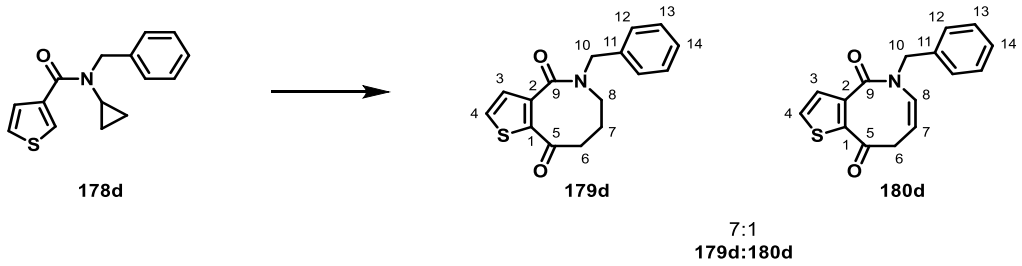
Data for minor compound **180c**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ 6.15 (1H, d, *J* = 7.5 Hz, C**8**-H), 5.61 (1H, ddd, *J* = 10.0, 7.5, 7.0 Hz, C**7**-H), 5.25 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 4.48 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 3.26 (1H, dd, *J* = 12.5, 10.0 Hz, 1 × C**6**-H_2), 2.98 (1H, dd, *J* = 12.5, 7.0 Hz, 1 × C**6**-H_2).

***N*-Benzyl-*N*-cyclopropylthiophene-3-carboxamide (178d)**



General Procedure B: Thiophene-3-carboxylic acid (256 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (309 mg, 2.10 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (20% EtOAc/ hexane) to give the title compound **178d** (350 mg, 68%) as a colourless oil; ν_{max}/ cm^{-1}: 3086 (m), 1618 (s), 1417 (s), 1294 (m), 1259 (m), 1028 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (1H, m, C**4**-H), 7.43 – 7.24 (7H, m, C**1**-H, C**3**-H, 2 × C**8**-H, 2 × C**9**-H and C**10**-H), 4.78 (2H, s, C**6**-H_2), 2.72 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-H), 0.74 – 0.56 (4H, m, 2 × C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ167.7 (C**5**), 138.0, 137.9 (C**2** and C**7**), 128.7, 128.0 127.9, 127.8, 127.4, (C**3**, C**4**, C**8**, C**9** and C**10**), 125.0 (C**1**), 51.2 (C**6**), 31.3 (C**11**), 9.9 (C**12**); HRMS: $(ESI)^+$ Calculated for $C_{15}H_{16}NOS$: 258.0947. Found $[M + H]^+$: 258.0958.

5-Benzyl-5,6,7,8-tetrahydrothieno[3,2-*c*]azocine-4,9-dione (179d) and **(*Z*)-5-Benzyl-5,8-dihydrothieno[3,2-*c*]azocine-4,9-dione (180d)**

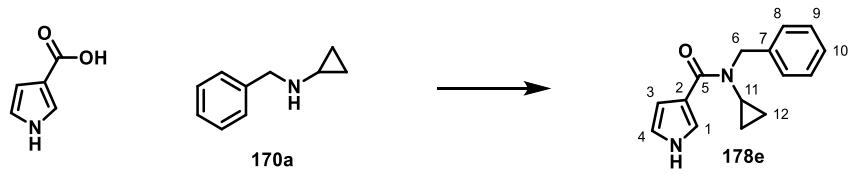


General Procedure C: Thiophene **178d** (38.6 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The residue was purified by flash column chromatography (15% Et_2O/toluene) to yield the title compound **179d** (24.2 mg, 57%) as a colourless oil and **180d** (3.40 mg, 8%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 7:1 (**179d: 180d**) mixture of products.

Data for major compound **179d**: ν_{max}/ cm^{-1}: 3089 (m), 2915 (m), 1675 (s), 1627 (s), 1524 (m), 1418 (s) 1253 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, d, *J* = 5.0 Hz, C**4**-H), 7.43 (1H, d, *J* = 5.0 Hz, C**3**-H), 7.40 – 7.27 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 5.19 (1H, br. m, 1 × C**10**-H_2), 4.46 (1H, br. m, 1 × C**10**-H_2), 3.67 – 3.35 (2H, br. m, C**8**-H_2), 3.95 – 2.61 (2H, br. m, C**6**-H_2), 2.19 – 1.69 (2H, br. m, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.5 (C**5**), 166.0 (C**9**), 143.7 (C**1**), 138.8 (C**2**), 137.0 (C**11**), 133.4 (C**4**), 132.4 (C**3**), 129.0 (C**13**), 128.5 (C**12**), 128.1 (C**14**), 48.8 (C**10**), 45.8 (C**8**), 36.9 (C**7**), 25.8 (C**6**); HRMS: $(ESI)^+$ Calculated for $C_{16}H_{16}NO_2S$: 286.0896. Found $[M + H]^+$: 286.0904.

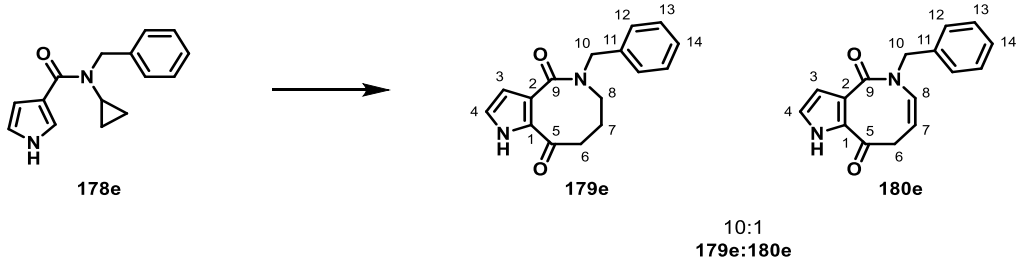
Data for minor compound **180d**: ν_{max}/ cm^{-1}: 3085 (m), 2926 (m), 1653 (s), 1626 (s), 1517 (m), 1470 (m), 1439 (s), 1406 (s), 1264 (m), 1227 (m), 1160 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, d, *J* = 5.0 Hz, C**4**-H), 7.42 – 7.28 (6H, m, C**3**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.16 (1H, dd, *J* = 7.5, 1.0 Hz, C**8**-H), 5.68 (1H, ddd, *J* = 10.0, 7.5, 7.0 Hz, C**7**-H), 5.24 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 4.55 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 3.39 (1H, ddd, *J* = 12.5, 10.0, 1.0 Hz, 1 × C**6**-H_2), 3.04 (1H, dd, *J* = 12.5, 7.0 Hz, 1 × C**6**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.2 (C**5**), 164.6 (C**9**), 140.2 (C**1**), 138.5 (C**2**), 136.3 (C**11**), 132.6 (C**3**), 131.9 (C**4**), 131.5 (C**8**), 128.9 (C**13**), 128.7 (C**12**), 128.2 (C**14**), 122.2 (C**7**), 51.5 (C**10**), 40.7 (C**6**); HRMS: $(ESI)^+$ Calculated for $C_{16}H_{14}NO_2S$: 284.0740. Found $[M + H]^+$: 284.0749.

***N*-Benzyl-*N*-cyclopropyl-1*H*-pyrrole-3-carboxamide (179e)**



General Procedure B: 1*H*-Pyrrole-3-carboxylic acid (444 mg, 4.00 mmol) and *N*-benzylcyclopropylamine **170a** (618 mg, 4.20 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (5% EtOAc/ CH_2Cl_2) to give the title compound **178d** (725 mg, 74%) as a colourless solid; m.p.: 82–84 °C (ethanol); ν_{max}/ cm^{-1}: 3189 (br. m), 3032 (m), 1588 (s), 1538 (m), 1496 (m), 1410 (s), 1364 (m), 1200 (m), 1080 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (1H, s, NH), 7.36 – 7.20 (6H, m, C**1**-H, 2 × C**8**-H, 2 × C**9**-H and C**10**-H), 6.67 (1H, m, C**4**-H), 6.61 (1H, m, C**3**-H), 4.79 (2H, s, C**6**-H_2), 2.79 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-H), 0.81 – 0.64 (4H, m, 2 × C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0 (C**5**), 138.8 (C**7**), 128.6, 127.7 (C**8** and C**9**), 127.1 (C**10**), 122.8 (C**1**), 119.5 (C**2**), 117.9 (C**4**), 109.9 (C**3**), 51.5 (C**6**), 31.3 (C**11**), 10.4 (C**12**); HRMS: $(ESI)^+$ Calculated for $C_{15}H_{17}N_2O$: 241.1335. Found $[M + H]^+$: 241.1343.

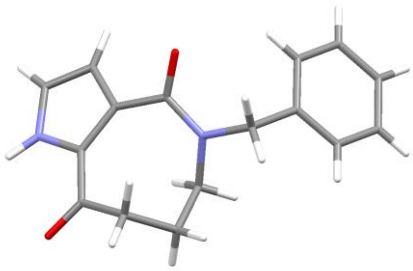
5-Benzyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azocine-4,9-dione (179e) and **(*Z*)-5-Benzyl-5,8-dihydro-1*H*-pyrrolo[3,2-*c*]azocine-4,9-dione (180e)**



General Procedure C: Pyrrole **178e** (36.0 mg, 0.15 mmol) was employed and the reaction mixture was heated at 130 °C for 72 h. The residue was purified by flash column chromatography (50%

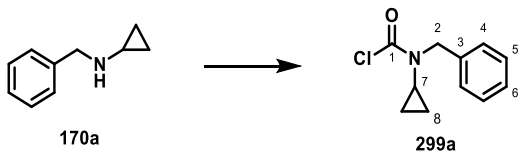
EtOAc/hexane) to yield the title compound **179e** (28.9 mg, 72%) as a colourless solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 10:1 (**179e**:**180e**) mixture of products. The minor product **180e** was not isolated.

Data for major compound **179e**: m.p.: 176–179 °C (CH_2Cl_2/hexane); ν_{max}/ cm^{-1}: 3246 (br. m), 2934 (m), 1638, (s) 1591 (s), 1541 (s), 1495 (s), 1461 (s), 1402 (s), 1117 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (1H, br. s, NH), 7.40 – 7.28 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.01 (1H, dd, *J* = 3.0, 3.0 Hz, C**4**-H), 6.72 (1H, dd, *J* = 3.0, 3.0 Hz, C**3**-H), 5.07 (1H, br. m, 1 × C**10**-H_2), 4.50 (1H, br. m, 1 × C**10**-H_2), 3.80 (1H, br. m, 1 × C**8**-H_2), 3.30 (1H, br. m, 1 × C**8**-H_2), 2.92 (1H, br. m, 1 × C**6**-H_2), 2.50 (1H, br. m, 1 × C**6**-H_2), 1.95 (1H, br. m, 1 × C**7**-H_2), 1.79 (1H, br. m, 1 × C**7**-H_2); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 11.72 (1H, br. s, NH), 7.38 – 7.26 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.05 (1H, d, *J* = 2.5 Hz, C**4**-H), 6.46 (1H, d, *J* = 2.5 Hz, C**3**-H), 4.73 (2H, s, C**10**-H_2), 3.44 (2H, t, *J* = 6.5 Hz, C**8**-H_2), 2.56 (2H, t, *J* = 6.5 Hz, C**6**-H_2), 1.83 (2H, tt, *J* = 6.5, 6.5 Hz, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$, 20 °C): δ 189.7 (C**5**), 167.1 (C**9**), 137.6 (C**11**), 130.5 (C**1**), 128.9, 128.4, 127.8 (C**12**, C**13** and C**14**), 124.2 (C**2**), 123.8 (C**4**), 114.4 (C**3**), 48.8 (C**10**), 46.1 (C**8**), 36.5 (C**6**), 26.2 (C**7**). HRMS: (ESI)$^{+}$ Calculated for $C_{16}H_{16}N_2NaO$: 291.1104. Found [M + Na]$^{+}$: 292.1110. *A ^{1}H NMR spectrum was recorded at 100 °C in DMSO-d_6 because at room temperature slow conformational interconversion gave a broad spectrum. The structure of this compound was determined unambiguously by X-ray cystrallography.*



Data for minor compound **180e**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ 6.12 (1H, d, *J* = 7.5 Hz, C**8**-H), 5.62 (1H, dt, *J* = 10.0, 7.5 Hz, C**7**-H).

Benzyl(cyclopropyl)carbamic chloride (299a)

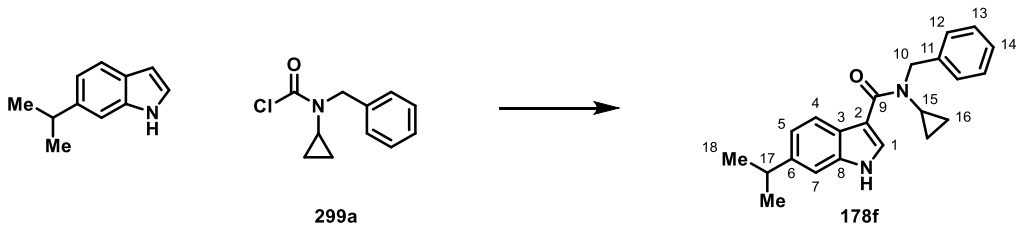


170a 299a

Pyridine (0.97 mL, 12.0 mmol) was added dropwise over 10 minutes to a solution of triphosgene (1.08 g, 3.60 mmol) in toluene (33 mL) at 0 °C. To the resulting suspension was added a solution of *N*-benzylcyclopropanamine **170a** (1.47 g, 10.0 mmol) in toluene (5 mL) and the reaction was warmed

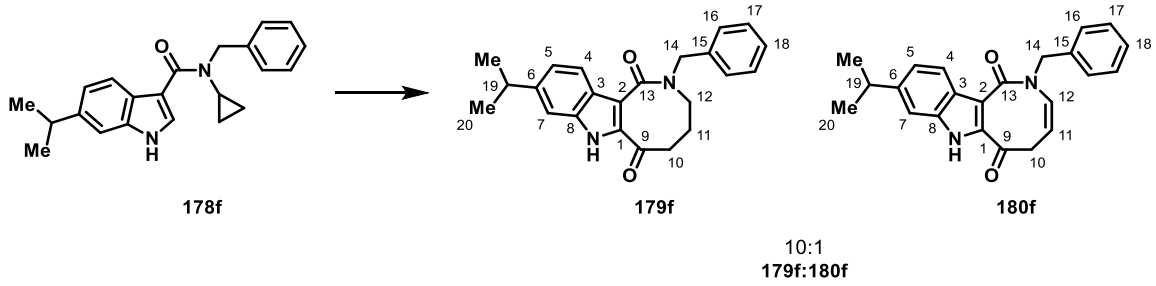
to room temperature. After 2 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with Et_2O (2 × 40 mL). The organic layers were combined and washed with 0.2 M aqueous HCl (30 mL), H_2O (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound **299a** (1.98 g, 95%) as a yellow oil. The crude material was used without further purification. ν_{max}/ cm^{-1}: 3092 (m), 3063 (m), 1454, (s) 1375 (s), 1232 (s), 1199 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.21 (5H, m, 2 × C**4**-H, 2 × C**5**-H and C**6**-H), 4.60 (2H, s, C**2**-H_2), 2.74 – 2.57 (1H, m, C**7**-H), 0.87 (4H, m, 2 × C**8**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.4 (C**1**), 136.2 (C**3**), 128.8, 127.9, 127.7 (C**4**, C**5** and C**6**), 53.7 (C**2**), 32.5 (C**7**), 10.0 (C**8**). *The spectroscopic properties of this compound were consistent with the data available in literature.*[343]

***N*-Benzyl-*N*-cyclopropyl-6-isopropyl-1*H*-indole-3-carboxamide (178f)**



To a suspension of 6-isopropyl-1*H*-indole (212 mg, 1.33 mmol) and $AlCl_3$ (214 mg, 1.61 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a solution of benzyl(cyclopropyl)carbamic chloride **299a** (460 mg, 1.61 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred at 0 °C for 4 hours and then warmed to room temperature. The reaction mixture was quenched by addition of H_2O (40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was recrystallised from MeOH to afford the title compound **178f** (264 mg, 60%) as a white crystalline solid; m.p.: 192–195 °C (MeOH); ν_{max}/ cm^{-1}: 3192 (br. m), 2957 (m), 1592 (s), 1566 (m), 1529 (m), 1435 (s), 1368 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 9.13 (1H, br. s, NH), 7.94 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.36 (1H, d, *J* = 3.0 Hz, C**1**-H), 7.34 – 7.21 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.14 – 7.06 (2H, m, C**5**-H and C**7**-H), 4.83 (2H, s, C**10**-H_2), 2.95 (1H, hept, *J* = 7.0 Hz, C**17**-H), 2.68 (1H, tt, *J* = 6.0, 5.0 Hz, C**15**-H), 1.26 (6H, d, *J* = 7.0 Hz, 2 × C**18**-H_3), 0.71 – 0.60 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1 (C**9**), 144.1 (C**6**), 138.7 (C**11**), 136.1 (C**8**), 128.7, 127.9, 127.4, 127.2 (C**1**, C**12**, C**13** and C**14**), 125.1 (C**3**), 121.2 (C**4**), 120.7 (C**5**), 111.7 (C**2**), 108.7 (C**7**), 51.7 (C**10**), 34.3 (C**17**), 30.8 (C**15**), 24.5 (C**18**), 10.2 (C**16**); HRMS: $(ESI)^+$ Calculated for $C_{22}H_{24}N_2O$: 333.1961. Found $[M + H]^+$: 333.1962.

2-Benzyl-9-isopropyl-2,3,4,5-tetrahydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (179f) and **(*Z*)-2-Benzyl-9-isopropyl-2,5-dihydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (180f)**

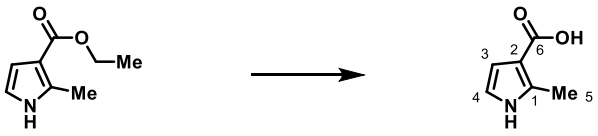


General Procedure C: Indole **178f** (33.2 mg, 0.10 mmol) was employed and the reaction mixture was heated at 130 °C for 72 h. The residue was purified by flash column chromatography (5–10% acetone/toluene) to yield the title compound **179f** (18.3 mg, 51%) as a yellow solid and **180f** (1.70 mg, 5%) as a colourless oil. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 10:1 (**179f**:**180f**) mixture of products.

Data for major compound **179f**: m.p.: 205–208 °C (EtOAc/petroleum ether); ν_{max}/ cm^{-1}: 3248 (br. s), 2950 (m), 2925 (m), 1656 (s), 1607 (s), 1524 (s), 1457 (s), 1416 (s), 1212 (m), 1122 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (1H, br. s, NH), 8.04 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.46 – 7.25 (6H, m, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.20 (1H, d, *J* = 8.5 Hz, C**5**-H), 5.37 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 4.50 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.82 (1H, m, 1 × C**12**-H_2), 3.30 (1H, m, 1 × C**12**-H_2), 3.17 – 3.01 (2H, m, 1 × C**10**-H_2 and C**19**-H), 2.63 (1H, d, *J* = 12.5 Hz, 1 × C**10**-H_2), 2.08 (1H, m, 1 × C**11**-H_2), 1.86 (1H, m, 1 × C**11**-H_2), 1.32 (6H, d, *J* = 7.0 Hz, 2 × C**20**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 191.9 (C**9**) 166.5 (C**13**), 149.2 (C**6**), 137.5 (C**15**), 136.7 (C**8**), 133.3 (C**1**), 128.9, 128.3, 127.8 (C**16**, C**17** and C**18**), 126.5 (C**3**), 123.5 (C**4**), 122.4 (C**5**), 115.2 (C**2**), 108.8 (C**7**), 48.4 (C**14**), 45.7 (C**12**), 36.8 (C**10**), 34.7 (C**19**), 26.4 (C**11**), 24.2 (C**20**); HRMS: (ESI)$^+$ Calculated for $C_{23}H_{24}N_2O$: 361.1911. Found [M + H] $^+$: 361.1913.

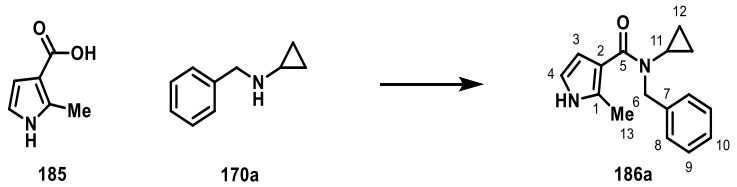
Data for minor compound **180f**: ν_{max}/ cm^{-1}: 3297 (br. m), 2951 (m), 2926 (m), 1672 (s), 1622 (s), 1523 (s), 1384 (s), 1265 (s), 1229 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (1H, br. s, NH), 7.94 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.43 – 7.40 (2H, m, 2 × C**16**-H), 7.37 – 7.33 (2H, m, 2 × C**17**-H), 7.31 (1H, m, C**18**-H), 7.22 (1H, d, *J* = 1.5 Hz, C**7**-H), 7.17 (1H, dd, *J* = 8.5, 1.5 Hz, C**5**-H), 6.13 (1H, d, *J* = 7.5 Hz, C**12**-H), 5.62 (1H, ddd, *J* = 10.0, 7.5, 6.5 Hz, C**11**-H), 5.25 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 4.81 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.53 (1H, dd, *J* = 12.5, 10.0 Hz, 1 × C**10**-H_2), 3.09 (1H, dd, *J* = 12.5, 6.5 Hz, 1 × C**10**-H_2), 3.02 (1H, hept, *J* = 7.0 Hz, C**19**-H), 1.30 (6H, d, *J* = 7.0 Hz, 2 × C**20**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$) 5δ 189.0 (C**9**), 164.2 (C**13**), 148.9 (C**6**), 136.9 (C**15**), 136.3 (C**8**), 131.9 (C**12**), 130.5 (C**1**), 128.9 (C**16**), 128.5 (C**17**), 127.9 (C**18**), 126.9 (C**3**), 123.5 (C**4**), 122.4 (C**5**), 120.6 (C**11**), 114.8 (C**2**), 108.7 (C**7**), 51.3 (C**14**), 40.2 (C**10**), 34.5 (C**19**), 24.25 (C**20**); HRMS: (ESI)$^+$ Calculated for $C_{23}H_{22}N_2O$: 359.1754. Found [M + H] $^+$: 359.1755.

Methyl-1*H*-pyrrole-3-carboxylic acid (185)



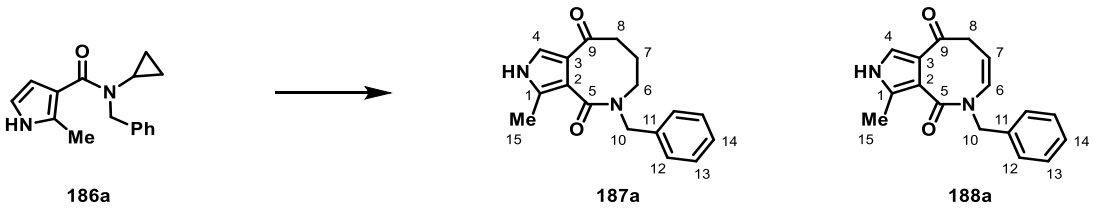
To a stirred solution of ethyl 2-methyl-pyrrole-3-carboxylate (1.00 g, 6.50 mmol) in 1,4-dioxane (10.0 mL) and water (5.0 mL) was added lithium hydroxide monohydrate (0.50 g, 12.0 mmol). The reaction mixture was heated at reflux for 4 hours and then cooled to room temperature. The mixture was acidified to pH 2 with 2 M aqueous HCl and then extracted into EtOAc (2 × 30 mL). The organic extracts were combined, washed with H_2O (30 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound **185** as an off-white solid (800 mg, 98%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.49 (1H, br. s, COOH), 11.07 (1H, br. s, N<u>H</u>), 6.56 (1H, m, C**4**-<u>H</u>), 6.28 (1H, dd, *J* = 2.5, 2.5 Hz, C**3**-<u>H</u>), 2.39 (3H, s, C**5**-<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4 (C**6**), 134.4 (C**4**), 115.7 (C**1**), 110.4 (C**3**), 109.7 (C**2**) 12.5 (C**5**). *The spectroscopic properties of this compound are in agreement with the literature.*[344]

***N*-Benzyl-*N*-cyclopropyl-2-methyl-1*H*-pyrrole-3-carboxamide (186a)**



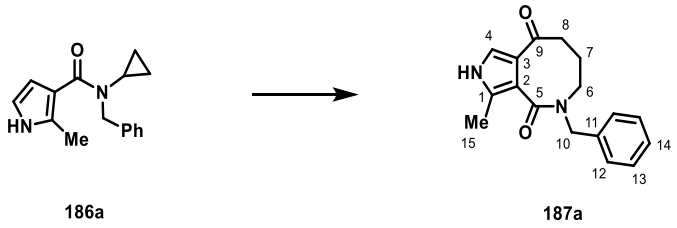
<u>General Procedure B:</u> 2-Methyl-1*H*-pyrrole-3-carboxylic acid **185** (375 mg, 3.00 mmol) and *N*-benzylcyclopropylamine **170a** (485 mg, 3.30 mmol) were employed and the reaction was stirred at room temperature for 4 hours. The crude residue was purified by flash column chromatography (30% EtOAc/CH_2Cl_2) to give the title compound **186a** (305 mg, 40%) as a colourless oil; ν_{max}/ cm^{-1}: 3240 (br. m), 2924 (m), 1598 (s), 1494 (s), 1401 (s), 1368 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (1H, br. s, N<u>H</u>), 7.37 – 7.19 (5H, m, 2 × C**8**-<u>H</u>, 2 × C**9**-<u>H</u> and C**10**-<u>H</u>), 6.45 (1H, dd, *J* = 3.5, 3.0 Hz, C**4**-<u>H</u>), 6.30 (1H, tt, *J* = 3.5, 3.0 Hz, C**3**-<u>H</u>), 4.75 (2H, s, C**6**-<u>H</u>$_2$), 2.65 (1H, tt, *J* = 7.0, 3.5 Hz, C**11**-<u>H</u>), 2.31 (3H, s, C**13**-<u>H</u>$_3$), 0.72 – 0.56 (4H, m, 2 × C**12**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6 (C**5**), 138.7 (C**7**), 132.4 (C**1**), 128.6, 127.8, 127.1 (C**8**, C**9** and C**10**), 115.3, 115.2 (C**2** and C**4**), 109.1 (C**3**), 51.6 (C**6**), 30.8 (C**11**), 12.7 (C**13**), 9.7 (C**12**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{18}N_2NaO$: 277.1311. Found [M + Na]$^+$: 277.1314.

5-Benzyl-3-methyl-5,6,7,8-tetrahydro-2H-pyrrolo[3,4-*c*]azocine-4,9-dione (187a) and **(*Z*)-5-Benzyl-3-methyl-5,8-dihydro-2H-pyrrolo[3,4-*c*]azocine-4,9-dione (188a)**



General Procedure C: *In a modification to general procedure C, [Rh(cod)OMe]$_2$ (3.75 mol%), P(4-(F)C$_6$H$_4$)$_3$ (22.5 mol%) and 2-nitrobenzoic acid (150 mol%) were dissolved in argon sparged anhydrous PhCN (0.10 M).* Pyrrole **186a** (38.1 mg, 0.15 mmol) was employed and the reaction mixture was heated at 130 °C for 72 h. The residue was purified by flash column chromatography (20–70% EtOAc/toluene) to yield the title compound **187a** (10.5 mg, 25%) as an off white solid and the title compound **188b** (5.04 mg, 12%) as a colourless oil.

*Alternatively, a two-step reaction sequence was more effective for the conversion of pyrrole **186a** to **187a.***



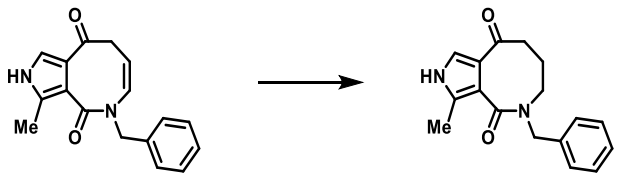
An oven dried reaction tube, fitted with a magnetic stirrer, was charged with [Rh(cod)OMe]$_2$ (2.72 mg, 5.62 µmol), P(4-(F)C$_6$H$_4$)$_3$ (10.6 mg, 33.7 µmol), 1-adamantanecarboxylic acid (40.5 mg, 0.225 mmol) and amide substrate **186a** (38.1 mg, 0.15 mmol). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged anhydrous PhCN (0.50 mL). The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds, then heated at 130 °C under a CO atmosphere for 72 h. The mixture was cooled to room temperature, filtered through a short plug of silica and concentrated *in vacuo*. To the residue was added xantphos (17.4 mg, 30 µmol) and [Rh(cod)$_2$]BARF (8.9 mg, 7.5 µmol), followed by the addition of anhydrous mesitylene (2.0 mL). The resulting suspension was sparged with hydrogen for approximately 60 seconds and then heated under a hydrogen atmosphere (1 atm) at 120 °C for 3 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (90% EtOAc/hexane) to yield the title compound **187a** (25.4 mg, 58%) as an off white solid.

Data for compound **187a**: m.p.: 177–180 °C (CH_2Cl_2/hexane); ν_{max}/ cm^{-1}: 3209 (br. m), 2926 (m), 1646 (m), 1601 (s) 1514 (s), 1445 (s), 1119 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (1H, br. s, N<u>H</u>), 7.35 –

7.27 (6H, m, C**4**-H, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 5.27 (1H, br. m, 1 × C**10**-H_2), 4.31 (1H, br. m, 1 × C**10**-H_2), 3.73 (1H, br. m, 1 × C**6**-H_2), 3.21 (1H, br. m, 1 × C**6**-H_2), 2.85 (1H, br. m, 1 × C**8**-H_2), 2.36 (4H, br. m, 1 × C**8**-H_2 and C**15**-H_3), 2.04 (2H, br. m, C**7**-H_2); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 11.48 (1H, br. s, NH), 7.34 – 7.14 (6H, m, C**4**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 4.70 (2H, s, C**10**-H_2), 3.40 (2H, br. m, C**6**-H_2), 2.46 (2H, br. m, C**8**-H_2), 2.29 (3H, s, C**15**-H_3), 1.84 – 1.74 (2H, m, C**7**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$, 20 °C): δ 196.5 (C**9**), 168.0 (C**5**), 137.6 (C**11**), 134.7 (C**1**), 128.8, 128.1 (C**12** and C**13**), 127.7 (C**14**), 125.9 (C**3**), 121.7 (C**4**), 114.3 (C**2**), 48.2 (C**10**), 45.4 (C**6**), 37.7 (C**8**), 25.5 (C**7**), 12.7 (C**15**); ^{13}C NMR (126 MHz, DMSO-d_6, 100 °C) δ 194.0 (C**9**), 166.4 (C**5**), 138.0 (C**11**), 133.1 (C**1**), 127.8, 127.3, 126.5 (C**12**, C**13** and C**14**), 124.5 (C**3**), 120.4 (C**4**), 113.6 (C**2**), 46.9 (C**10**), 44.6 (C**6**), 36.8 (C**8**), 24.5 (C**7**), 11.4 (C**15**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{18}N_2NaO_2$: 305.1265. Found $[M + Na]^+$: 305.1260. *A ^{1}H NMR spectrum was recorded at 100 °C in DMSO-d_6 because at room temperature slow conformational interconversion gave a broad spectrum. The signals for C**6**-H_2, C**7**-H_2 and C**8**-H_2, coalesced at 100 °C but they were not resolved.*

Data for compound **188a**: ν_{max}/ cm^{-1}: 3176 (br. m), 1659 (s), 1624 (s), 1578 (s), 1514 (s), 1448 (s), 1122 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (1H, br. s, NH), 7.37 – 7.27 (6H, m, C**4**-H, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 6.08 (1H, d, *J* = 7.0 Hz, C**6**-H), 5.59 (1H, m, C**7**-H), 5.06 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 4.65 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 3.36 (1H, m, 1 × C**8**-H_2), 2.87 (dd, *J* = 12.0, 6.5 Hz, 1 × C**8**-H_2), 2.35 (3H, s, C**15**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.1 (C**9**), 166.2 (C**5**), 136.9 (C**11**), 133.7 (C**1**), 131.3 (C**6**), 128.8, 128.5, 127.8, (C**12**, C**13** and C**14**), 122.2 (C**7**), 121.6 (C**3**), 121.2 (C**4**), 115.1 (C**2**), 51.0 (C**10**), 41.9 (C**8**), 12.8 (C**15**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{16}N_2NaO_2$: 303.1104. Found $[M + Na]^+$: 303.1106.

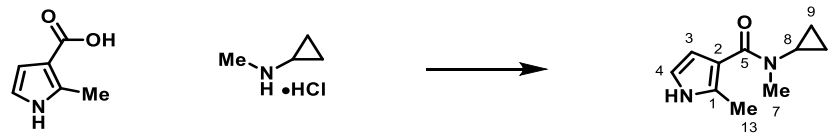
*The use of Pd/C and H_2 (1 atm) was also effective for the conversion of enamide **188a** to **187a.***



188a **187a**

To a solution of enamide **188a** (28.0 mg, 0.10 mmol) in MeOH (5 mL) was added 20% Pd/C (5.6 mg, 20 wt.%). The reaction flask was evacuated and backfilled with H_2 three times and then stirred at room temperature with the hydrogen balloon attached. The reaction mixture was monitored by TLC analysis and upon completion (~ 2 hours), the reaction was filtered through Celite® and concentrated *in vacuo*. Purification by flash column chromatography (90%EtOAc/hexane) afforded the title compound **187a** (25.0 mg, 89%) as an off white solid.

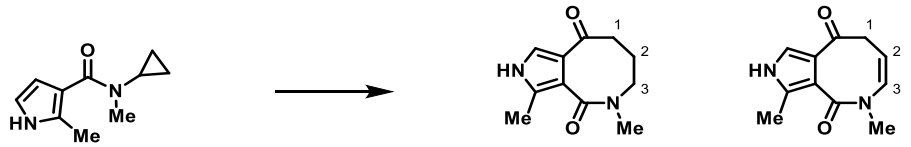
***N*-cyclopropyl-N,2-dimethyl-1H-pyrrole-3-carboxamide (186b)**



185 186b

General Procedure B: *In a modification to general procedure B, Et_3N (1.27 mL, 9.20 mmol) was used instead of DMAP.* 2-Methyl-1*H*-pyrrole-3-carboxylic acid **185** (575 mg, 4.60 mmol) and *N*-methylcyclopropanamine hydrochloride (596 mg, 5.57 mmol) (prepared according to the literature procedure[345]) were employed and the reaction was stirred at room temperature for 16 hours. The residue was purified by flash column chromatography (10–90% EtOAc/hexane) to afford the title compound **186b** (344 mg, 42%) as a colourless oil; ν_{max}/ cm^{-1}: 3223 (br. s), 2929 (m), 1590 (s), 1491 (s), 1384 (s), 1358 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (1H, br. s, NH), 6.45 (1H, t, *J* = 2.5 Hz, ArC-H), 6.27 (t, *J* = 2.5 Hz, ArC-H), 3.03 (3H, s, C**7**-H_3), 2.83 (1H, tt, *J* = 7.0, 4.0 Hz, C**8**-H), 2.26 (3H, s, C**13**-H_3), 0.88 – 0.48 (4H, m, 2 × C**9**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5 (C**5**), 132.2 (ArC), 115.3, 115.02, 109.6 (Ar-CH), 32.4 (C**8**), 12.6, (2 signals, C**7** and C**13**), 9.0 (C**9**); HRMS: $(ESI)^+$ Calculated for $C_{10}H_{15}N_2O$: 178.1109. Found $[M + H]^+$: 178.1109.

3,5-Dimethyl-5,6,7,8-tetrahydro-2H-pyrrolo[3,4-*c*]azocine-4,9-dione and **(*Z*)-3,5-Dimethyl-5,8-dihydro-2H-pyrrolo[3,4-*c*]azocine-4,9-dione**



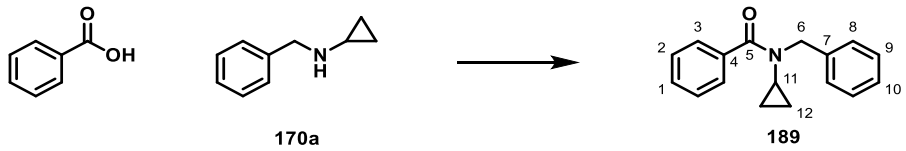
186b 187b 188b

General Procedure C: *In a modification to General procedure C 1-adamantanecarboxylic acid (50 mol%) was used instead of 2-$NO_2C_6H_4COOH$ (150 mol%).* Pyrrole **186b** (26.5 mg, 0.15 mmol) was employed and the reaction mixture was heated at 130 °C for 72 h. The conversion to products **187b**/**188b** was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. This revealed 28% **187b** and 26% **188b**. Products **187b**/**188b** were not isolated. *The structural assignment of **187b**/**188b** was determined by comparison to analogous products.*

Data for product 1**87b**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): 3.87 (1H, m, 1 × C**3**-H_2), 1.80 (1H, m, 1 × C**1**-H_2).

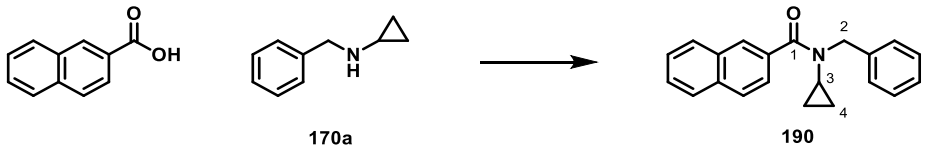
Data for product 1**88b**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (1H, d, *J* = 7.5 Hz, C**3**-H), 5.56 (1H, dt, *J* = 10.0, 7.5 Hz, C**2**-H).

***N*-Benzyl-*N*-cyclopropylbenzamide (189)**



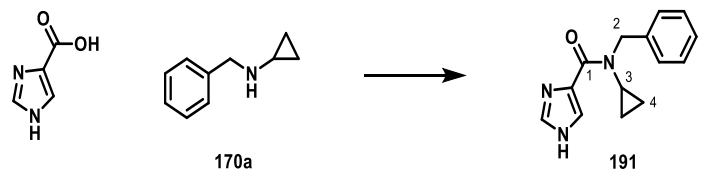
General Procedure B: Benzoic acid (244 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (309 mg, 2.10 mmol) were employed and the reaction was stirred at r.t. for 18 hours. The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to give the title compound **189** (388 mg, 78%) as a colourless oil; ν_{max}/ cm^{-1}: 3027 (m), 1632 (s), 1446 (s), 1401 (s), 1371 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.46 (2H, m, 2 × C**3**-H), 7.43 – 7.32 (6H, m, 6 × ArC-H), 7.29 (2H, m, 2 × ACr-H), 4.75 (2H, s, C**6**-H_2), 2.59 (1H, tt, *J* = 7.0, 4.0 Hz, C**11**-H), 0.55 – 0.49 (4H, m, 2 × C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2 (C**5**), 138.0, 137.5 (C**4** and C**7**), 129.7, 128.7, 128.3 (2 signals), 127.4, 127.3 (6 × Ar-CH), 51.0 (C**6**), 31.8 (C**11**), 10.0 (C**12**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{18}NO$: 252.1383. Found $[M + H]^+$: 252.1385.

***N*-benzyl-*N*-cyclopropyl-2-naphthamide (190)**



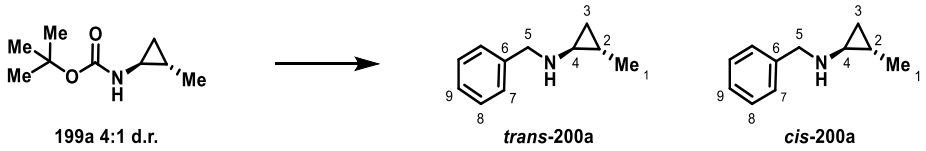
General Procedure B: 2-Naphthoic acid (172 mg, 1.00 mmol) and *N*-benzylcyclopropylamine **170a** (154 mg, 1.05 mmol) were employed and the reaction was stirred at r.t. for 18 hours. The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to give the title compound **190** (255 mg, 84%) as a white solid; ν_{max}/ cm^{-1}: 3027 (m), 1630 (s), 1446 (s), 1401 (s), 1371 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, s, ArC-H), 7.90 – 7.82 (3H, m, 3 × ArC-H), 7.62 (1H, d, *J* = 8.0 Hz, ArC-H), 7.57 – 7.49 (2H, m, 2 × ArC-H), 7.46 – 7.29 (5H, m, 5 × ArC-H), 4.81 (2H, s, C**2**-H_2), 2.69 (1H, tt, *J* = 7.0, 3.0 Hz, C**3**-H), 0.52 (4H, br. m, 2 × C**4**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9 (C**1**), 134.8 (ArC), 134.8 (ArC), 134.7 (ArC), 132.7 (ArC), 128.8 (2 signals), 128.6, 128.2, 127.9, 127.5, 127.3, 127.1, 126.6, 124.7 (10 × Ar-CH), 50.9 (C**2**), 30.9 (C**3**), 10.3 (C**4**); HRMS: $(ESI)^+$ Calculated for $C_{21}H_{20}NO$: 303.1534. Found $[M + H]^+$: 303.1535.

***N*-benzyl-N-cyclopropyl-1H-imidazole-4-carboxamide (191)**



To a suspension of 1H-imidazole-4-carboxylic acid (297 mg, 2.20 mmol) in DMF (7 mL) was added HOBt (297 mg, 2.20 mmol) and Et_3N (0.86 mL, 6.20 mmol). The reaction mixture was stirred at room temperature for 30 minutes and then a solution of *N*-benzylcyclopropylamine **170a** (294mg, 2.00 mmol) in DMF (0.5 mL) was added. The resulting solution was stirred at room temperature for 18 hours and then CH_2Cl_2 (15 mL) was added. The solution was washed with water (3 × 50 mL), brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound **191** (226 mg, 47%) as a white solid; m.p.: 101–103 °C; ν_{max}/ cm^{-1}: 3125 (br. s), 1605 (s), 1437 (s), 1409 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 11.8 (1H, br. s. NH), 7.66 (1H, s, ArC-H), 7.49 (1H, s, ArC-H), 7.30 – 7.20 (5H, m, 5 × ArC-H), 4.79 (2H, s, C**2**-H_2), 2.91 (1H, m, C**3**-H), 1.08 – 0.68 (4H, m, 2 × C**4**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7 (C**1**), 137.9 (Ar-C) 137.2 (Ar-CH), 131.74 (ArC), 128.6, 127.3, 127.2 (3 × Ar-CH), 51.7 (C**2**), 31.1 (C**3**), 10.5 (C**4**); HRMS: $(ESI)^+$ Calculated for $C_{14}H_{17}N_3O$: 241.1215. Found $[M + H]^+$: 241.1211.

(1*S,2*S**)-*N*-Benzyl-2-methylcyclopropan-1-amine (*trans*-200a)** and **(1*S**,2*R**)-*N*-Benzyl-2-methylcyclopropan-1-amine (*cis*-200a)**

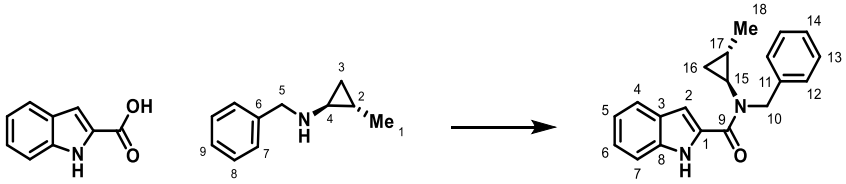


General procedure E: *N-Boc amine **199a** was synthesised by G.-W. Wang*. Boc-protected amine **199a** (2.29 g, 9.27 mmol) was employed and the residue was purified by flash column chromatography (0–30% EtOAc/hexane) to afford the title compound ***trans*-200a** (1.45 g, 80%) as a colourless oil and the *cis*-diastereomer ***cis*-200a** (250 mg, 13%) as colourless oils.

Data for ***trans*-200a**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.22 (5H, m, 2 × C**7**-H, 2 × C**8**-H and C**9**-H), 3.85 – 3.78 (2H, m, C**5**-H_2), 1.85 – 1.78 (2H, m, C**4**-H and NH), 0.98 (3H, d, *J* = 6.0 Hz, C**1**-H_3), 0.75 (1H, m, C**2**-H), 0.55 (1H, m, 1 × C**3**-H_2), 0.21 (1H, ddd, *J* = 6.5, 5.0, 5.0 Hz, 1 × C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7 (C**6**), 128.5, 128.4 (C**7** and C**8**), 127.0 (C**9**), 53.9 (C**5**), 38.4 (C**4**), 17.6 (C**1**), 14.9 (C**3**), 14.7 (C**2**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

Data for ***cis*-200a**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.22 (5H, m, 2 × C**7**-H, 2 × C**8**-H and C**9**-H), 3.85 – 3.78 (2H, m, C**5**-H_2), 2.15 (1H, ddd, *J* = 7.0, 7.0, 4.0 Hz, C**4**-H), 1.61 (1H, br. s, NH), 1.15 (3H, d, *J* = 6.0 Hz, C**1**-H_3), 0.76 (1H, m, C**2**-H), 0.63 (1H, ddd, *J* = 9.0, 7.0, 4.5 Hz, C**3**-H_2), 0.05 (1H, ddd, *J* = 6.0, 4.5, 4.0 Hz, C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.1 (C**6**), 128.5, 128.4 (C**7** and C**8**), 126.9 (C**9**), 54.3 (C**5**), 34.6 (C**2**), 13.2 (C**3**), 12.0 (2 signals, C**1** and C**2**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

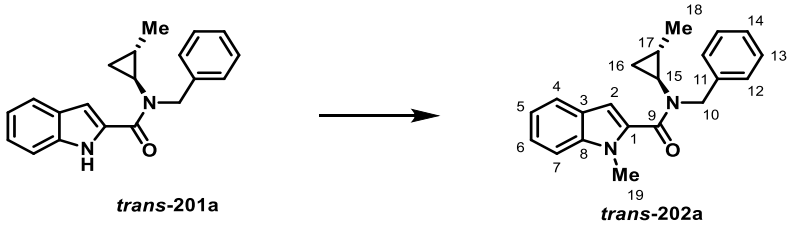
***N*-Benzyl-*N*-((1*S**, 2*S**)-2-methylcyclopropyl)-1*H*-indole-2-carboxamide (*trans*-201a)**



***trans*-200a** ***trans*-201a**

General Procedure B: 1*H*-Indole-2-carboxylic acid (1.61 g, 10 mmol) and (1*S**,2*S**)-*N*-benzyl-2-methylcyclopropan-1-amine ***trans*-200a** (1.61 g, 10 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (5-10% Et_2O/toluene) to give the title compound ***trans*-200a** (2.44 g, 80%) as a colourless solid; m.p.: 164–165 °C (ethanol); ν_{max}/ cm^{-1}: 3264 (br. m), 1602 (s), 1520 (s), 1434 (s), 1402 (s), 1348 (s), 1278 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (1H, br. s, NH), 7.66 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.43 – 7.23 (7H, m, C**6**-H, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.20 – 7.05 (2H, m, C**2**-H and C**5**-H), 4.95 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.83 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 2.67 (1H, ddd, *J* = 7.0, 4.0, 3.5 Hz, C**15**-H), 1.15 (1H, m, C**17**-H), 1.05 (3H, d, *J* = 6.0 Hz, C**18**-H_3), 0.95 (1H, ddd, *J* = 9.5, 5.5, 4.0 Hz, 1 × C**16**-H_2), 0.72 (1H, m, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.7 (C**9**), 138.0 (C**11**), 135.8 (C**8**), 130.3 (C**1**), 128.8 (C**13**), 127.9 (C**3**), 127.8, 127.4 (C**12** and C**14**), 124.7 (C**6**), 122.2 (C**4**), 120.4 (C**5**), 111.9 (C**7**), 107.2 (C**2**), 51.6 (C**10**), 38.8 (C**15**), 18.6, 18.0 (C**16** and C**17**), 17.5 (C**18**); HRMS: $(ESI)^+$ Calculated for $C_{20}H_{20}N_2NaO$: 327.1467. Found $[M + Na]^+$: 327.1479.

***N*-Benzyl-1-methyl-*N*-((1*S**, 2*S**)-2-methylcyclopropyl)-1*H*-indole-2-carboxamide (*trans*-202a)**

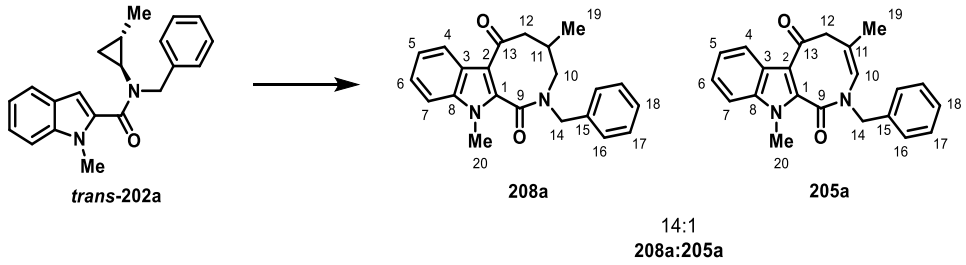


***trans*-201a** ***trans*-202a**

To a suspension of NaH (150 mg, 6.25 mmol, 60% dispersion in oil) in DMF (10.0 mL) at 0 °C was added indole ***trans*-200a** (950 mg, 3.13 mmol). After 15 minutes, iodomethane (0.23 mL, 3.75 mmol) was added dropwise over 10 minutes. The solution was then warmed to room temperature and stirred for 6 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (50 mL) and extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to give the title compound ***trans*-202a** (900 mg, 90%) as a yellow solid; m.p. 78–80 °C (EtOAc/ hexane); ν_{max}/ cm^{-1}: 2926 (m), 1632 (s), 1465 (s), 1408 (s), 1261 (s), 736 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.45 – 7.25 (7H, m, C**6**-H, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.14 (1H, m, C**5**-H), 6.76 (1H, s, C**2**-H), 4.96 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 4.63 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 3.88 (3H,

s, C**19**-H$_3$), 2.42 (1H, ddd, *J* = 7.0, 3.5, 3.5 Hz, C**15**-H), 0.99 – 0.69 (5H, m, 1 × C**16**-H$_2$, C**17**-H, C**18**-H$_3$), 0.47 (1H, m, 1 × C**16**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0 (C**9**), 138.1 (C**8**), 137.8 (C**11**), 133.1 (C**1**), 128.8, 128.1, 127.5 (C**12**, C**13** and C**14**), 126.6 (C**3**), 123.4 (C**6**), 121.7 (C**4**), 120.2 (C**5**), 109.9 (C**7**), 104.7 (C**2**), 51.1 (C**10**), 38.8 (C**15**), 31.4 (C**19**), 18.1 (C**17**), 17.0, 16.9 (C**18** and C**16**); HRMS: (ESI)$^+$ Calculated for $C_{21}H_{22}N_2NaO$: 341.1624. Found [M + Na] $^+$: 341.1639.

2-Benzyl-4,11-dimethyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (208a) and **(*Z*)-2-Benzyl-4,11-dimethyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (205a)**

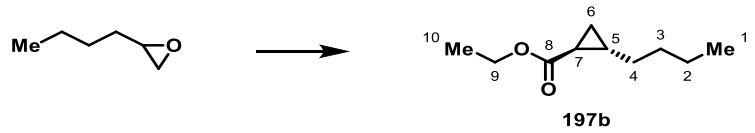


General Procedure F: Compound ***trans*-202a** (31.8 mg, 0.10 mmol), fumaric acid (11.6 mg, 0.10 mmol) and anhydrous benzonitrile (0.10 mL) were employed and the reaction mixture was heated at 140 °C for 72 hours. The crude mixture was purified by flash column chromatography (20% EtOAc/hexane then 10% toluene/hexane) to yield the title compound **208a** and compound **205a** (21.2 mg, 61%) as a colourless solid. ^{1}H NMR analysis revealed a 14:1 ratio of **208a**: **205a**. The minor product **205a** was not isolated.

Data for major product **208a**: m.p.: 128–130 °C (EtOAc/hexane); ν_{max}/ cm^{-1}: 2959 (m), 1718 (s), 1636 (s), 1506 (s), 1467 (s), 1389 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.42 – 7.30 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 5.44 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 4.37 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 3.90 (3H, s, C**20**-H$_3$), 3.53 (1H, m, 1 × C**10**-H$_2$), 3.23 – 3.14 (2H, m, 1 × C**10**-H$_2$ and 1 × C**12**-H$_2$), 2.49 – 2.29 (2H, m, C**11**-H and 1 × C**12**-H$_2$), 0.94 (3H, d, *J* = 7.0 Hz, C**19**-H$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.9 (C**13**), 163.6 (C**9**), 137.7 (C**8**), 136.8, 136.7 (C**1** and C**15**), 129.0, 128.2, 128.1 (C**16**, C**17** and C**18**), 125.4 (C**3**), 124.9 (C**6**), 124.1 (C**4**), 123.7 (C**5**), 117.8 (C**2**), 110.0 (C**7**), 52.4 (C**10**), 48.7 (C**14**), 44.4 (C**12**), 32.2 (C**20**), 31.2 (C**11**), 16.1 (C**19**); HRMS: (ESI)$^+$ Calculated for $C_{22}H_{23}N_2O_2$: 347.1754. Found [M + H] $^+$: 347.1753.

Data for minor product **205a**: *Characteristic signals only:* ^{1}H NMR (400 MHz, $CDCl_3$): 5.89 (1H, s, C**10**-H), 5.20 (1H, d, *J* = 14.0 Hz, 1 × C**14**-H$_2$), 4.78 (1H, d, *J* = 14.0 Hz, 1 × C**14**-H$_2$), 3.67 (1H, d, *J* = 12.0 Hz, 1 × C**12**-H$_2$), 2.86 (1H, d, *J* = 12.0 Hz, 1 × C**12**-H$_2$), 1.70 (3H, d, *J* = 1.5 Hz, 1 × C**19**-H$_3$)

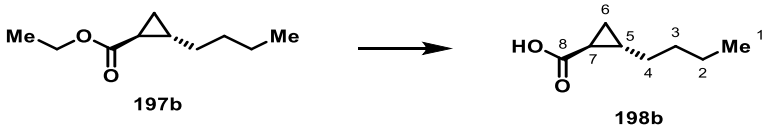
Ethyl (1*S, 2*S**)-2-butylcyclopropane-1-carboxylate (197b)**



197b

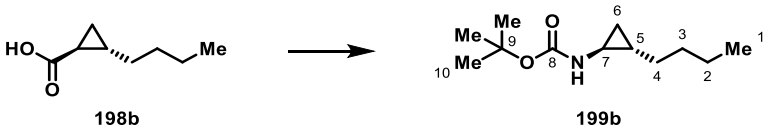
To a flame-dried screw-top reaction vessel, fitted with a rubber septum under an atmosphere of nitrogen was added anhydrous 1,2-dimethoxyethane (100 mL) and triethylphosphonacetate (11.8 mL, 59.0 mmol). The reaction vessel placed in an ice bath and *n*-BuLi (24.5 mL, 61.0 mmol, 2.5 M in hexanes) was added dropwise over 10 minutes. 2-Butyloxirane (3.61 mL, 30.0 mmol) was then added. The reaction vessel was sealed and heated at 130 °C for 16 hours. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (125 mL) was added. The reaction mixture was transferred to a separating funnel with Et_2O (75 mL) and the layers were separated. The aqueous layer was further extracted with Et_2O (3 × 100 mL). The organic layers were combined, washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOAc/hexane) to afford the title compound **197b** (4.15 g, 80%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (2H, q, *J* = 7.0 Hz, C**9**-$\underline{H}_2$), 1.43 – 1.28 (8H, m, C**2**-$\underline{H}_2$, C**3**-$\underline{H}_2$, C**4**-$\underline{H}_2$, C**5**-$\underline{H}$, C**7**-$\underline{H}$), 1.25 (3H, t, *J* = 7.0 Hz, C**10**-$\underline{H}_3$) 1.14 (1H, m, 1 × C**6**-$\underline{H}_2$), 0.89 (3H, t, *J* = 7.0 Hz, C**1**-$\underline{H}_3$), 0.67 (1H, ddd, *J* = 8.0, 6.0, 4.0 Hz, 1 × C**6**-$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.5 (C**8**), 60.1 (C**9**), 32.6 (C**4**), 31.1 (C**3**), 22.7 (C**5**), 22.2 (C**2**), 20.1 (C**7**), 15.4 (C**6**), 14.1 (C**10**), 13.9 (C**1**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[2]

(1*S, 2*S**)-2-Butylcyclopropane-1-carboxylic acid (198b)**



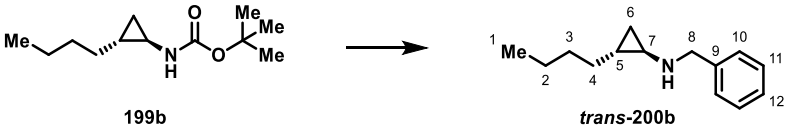
General Procedure D: Ester **197b** (4.10 g, 24.1 mmol) was employed to yield the title carboxylic acid **198b** (2.57 g, 75%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (8H, m, C**2**-$\underline{H}_2$, C**3**-$\underline{H}_2$, C**4**-$\underline{H}_2$, C**5**-$\underline{H}$ and C**7**-$\underline{H}$), 1.22 (1H, m, C**6**-$\underline{H}_2$), 0.89 (3H, t, *J* = 7.0 Hz, C**1**-$\underline{H}_3$), 0.77 (1H, ddd, *J* = 8.0, 6.5, 4.0 Hz, C**6**-$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.1 (C**8**), 32.9 (C**4**), 31.3 (C**3**), 24.2 (C**5**), 22.5 (C**2**), 20.2 (C**7**), 16.6 (C**6**), 14.2 (C**1**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

***tert*-Butyl ((1*S**, 2*S**)-2-butylcyclopropyl)carbamate (199b)**



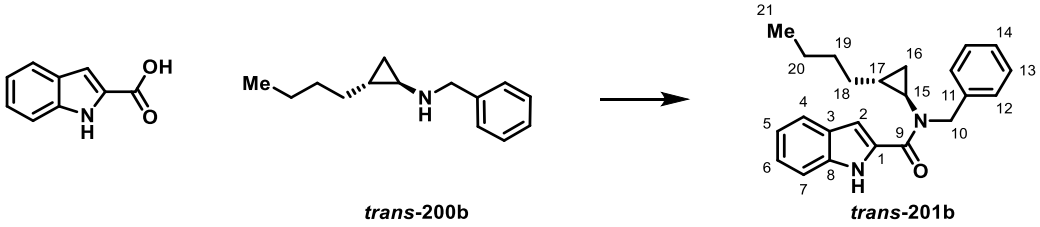
To a solution of carboxylic acid **198b** (2.82 g, 19.8 mmol) and Et_3N (3.03 mL, 21.8 mmol) in anhydrous *t*-BuOH (25 mL) was added diphenylphosphoryl azide (4.65 mL, 21.8 mmol) dropwise over 10 minutes. The reaction was heated at 80 °C for 36 hours, after which time the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Et_2O (50 mL) and saturated aqueous $NaHCO_3$ (150 mL) was added and the aqueous portion was extracted with Et_2O (3 × 75 mL). The organic extracts were combined, washed with water (75 mL), brine (75 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (5% EtOAc/toluene) to afford the title compound **199b** (3.35 g, 79%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65 (1H, br. s, N<u>H</u>), 2.23 (1H, m, C**7**-<u>H</u>), 1.43 (9H, s, 3 × C**10**-<u>H</u>$_3$), 1.39 – 1.33 (5H, m, C**2**-<u>H</u>$_2$, C**3**-<u>H</u>$_2$ and 1 × C**4**-<u>H</u>$_2$), 1.12 (1H, m, 1 × C**4**-<u>H</u>$_2$), 0.89 (3H, t, *J* = 7.5 Hz, C**1**-<u>H</u>$_3$), 0.80 (1H, m, C**5**-<u>H</u>), 0.59 (1H, m, 1 × C**6**-<u>H</u>$_2$), 0.47 (1H, m, 1 × C**6**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): 156.6 (C**8**), 79.4 (C**9**), 32.2 (C**4**), 31.3 (C**3**), 29.5 (C**7**), 28.6 (C**10**), 22.6 (C**2**), 20.8 (C**5**), 14.2 (C**6**), 13.9 (C**1**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

(1*S, 2*S**)-*N*-Benzyl-2-butylcyclopropan-1-amine (*trans*-200b)**



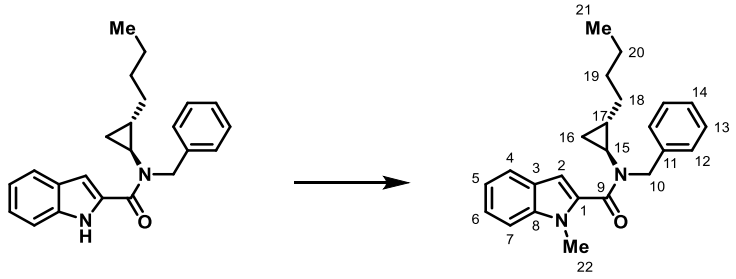
<u>General procedure E</u>: Boc-protected amine **199b** (2.29 g, 9.27 mmol) was employed and the residue was purified by flash column chromatography (20% EtOAC/toluene) to yield the title compound ***trans*-200b** (1.52 g, 81%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.17 (5H, m, 2 × C**10**-<u>H</u>, 2 × C**11**-<u>H</u> and C**12**-<u>H</u>), 3.77 (2H, s, C**8**-<u>H</u>$_2$), 1.82 (1H, ddd, *J* = 6.5, 3.5, 3.5 Hz, C**7**-<u>H</u>), 1.68 (1H, br. s, N<u>H</u>), 1.36 – 1.21 (4H, m, C**2**-<u>H</u>$_2$ and C**3**-<u>H</u>$_2$), 1.16 – 1.04 (2H, m, C**4**-<u>H</u>$_2$), 0.88 (3H, t, *J* = 7.0 Hz, C**1**-<u>H</u>$_3$), 0.71 (1H, m, C**5**-<u>H</u>), 0.49 (1H, ddd, *J* = 9.0, 4.5, 3.5 Hz, 1 × C**6**-<u>H</u>$_2$), 0.20 (1H, ddd, *J* = 6.5, 5.5, 4.5 Hz, 1 × C**6**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.6 (C**9**), 128.3, 128.2, 126.8 (C**10**, C**11** and C**12**), 53.7 (C**8**), 37.4 (C**7**), 32.3 (C**4**), 31.6 (C**3**), 22.5 (C**2**), 20.7 (C**5**), 14.1 (C**1**), 13.6 (C**6**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

***N*-Benzyl-*N*-((1*R**, 2*R**)-2-butylcyclopropyl)-1*H*-indole-2-carboxamide (*trans*-201b)**



General Procedure B: 1*H*-Indole-2-carboxylic acid (531 mg, 3.30 mmol) and amine ***trans*-200b** (704 mg, 3.47 mmol) were employed and the reaction was stirred at r.t. for 18 hours. The crude residue was purified by flash column chromatography (10% EtOAc/toluene) to give the title compound ***trans*-201b** (808 mg, 66%) as a colourless solid; m.p.: 141-143 °C (ethanol); ν_{max} / cm^{-1}: 3266 (br. s), 2921 (m), 1605 (s), 1521 (m), 1402 (m), 1278 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (1H, br. s, NH), 7.66 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.42 – 7.22 (7H, m, C**6**-H, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.20 – 7.06 (2H, m, C**2**-H and C**5**-H), 5.09 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.74 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 2.77 (1H, ddd, *J* = 7.0, 3.5, 3.5 Hz, C**15**-H), 1.45 (1H, m, 1 × C**18**-H_2), 1.34 – 1.22 (4H, m, C**19**-H_2 and C**20**-H_2), 1.21 – 1.04 (2H, m, C**17**-H and 1 × C**18**-H_2), 0.95 (1H, m, 1 × C**16**-H_2), 0.85 (3H, t, *J* = 7.0 Hz, C**21**-H_3), 0.79 (1H, m, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.8 (C**9**), 138.1 (C**11**), 135.8 (C**8**), 130.3 (C**1**), 128.8, 128.0, 127.5, 127.3 (C**3**, C**12**, C**13**, C**14**), 124.7 (C**6**), 122.2 (**C4**), 120.4 (C**5**), 111.9 (C**7**), 107.2 (C**2**), 51.8 (C**10**), 38.0 (C**15**), 32.3 (C**18**), 31.0 (C**20**), 23.1 (C**17**), 22.6 (C**19**), 14.2 (2 signals, C**16** and C**21**); HRMS: $(ESI)^+$ Calculated for $C_{24}H_{27}N_2O$: 347.2118. Found $[M + H]^+$: 347.2124.

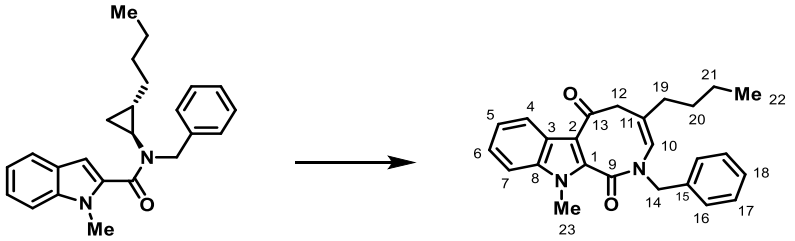
***N*-Benzyl-*N*-((1*S**,2*S**)-2-butylcyclopropyl)-1-methyl-1*H*-indole-2-carboxamide (*trans*-202b)**



To a suspension of NaH (73 mg, 3.02 mmol, 60% dispersion in oil) in DMF (10 mL) at 0 °C was added amide ***trans*-201b** (525 mg, 1.52 mmol). After 15 minutes, iodomethane (0.11 mL, 1.67 mmol) was added in dropwise over 5 minutes. The solution warmed to room temperature and stirred for 4 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (50 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to give the title compound ***trans*-202b** (500 mg, 91%) as a yellow oil; ν_{max}/ cm^{-1}: 2924 (m), 1630 (s), 1520 (m), 1464 (s), 1407 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.39 – 7.26 (7H, m, C**6**-H, C**7**-H, 2 × C**12**-H, 2 × C**13**-H, and C**14**-H), 7.12 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-H), 6.74 (1H, s, C**2**-H), 4.79 (2H, s, C**10**-H_2), 3.86 (3H, s, C**22**-H_3), 2.50 (1H, dt, *J* = 7.1, 3.6 Hz, C**15**-H), 1.20 – 0.98 (m, 5H, C**17**-H, C**18**-H_2 and C**19**-H_2), 0.98 – 0.69 (2H, m, C**20**-H_2), 0.81 – 0.69 (4H, m, 1 × C**16**-H_2 and C**21**-H_3), 0.50 (1H, m, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2 (C**9**), 138.1, 137.9 (C**8** and C**11**), 133.2 (C**2**), 128.8, 127.9, 127.5 (C**12**, C**13** and C**14**), 126.6 (C**3**), 123.4 (C**6**), 121.7 (C**4**), 120.2 (C**5**), 109.9 (C**7**), 104.6 (C**2**), 51.5

(C**10**), 37.9 (C**15**), 31.8 (C**18**), 31.4 (C**22**), 30.8 (C**19**), 23.2 (C**17**), 22.4 (C**20**), 16.3 (C**16**), 14.0 (C**21**); HRMS: (ESI)$^+$ Calculated for $C_{24}H_{29}N_2O$: 361.2274. Found [M + H]$^+$: 361.2268.

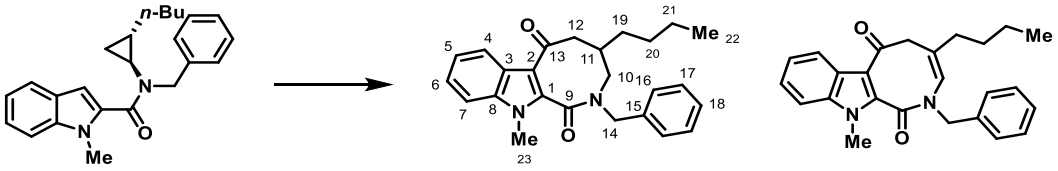
(*Z*)-2-Benzyl-4-butyl-11-methyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (205b)



***trans*-202b** **205b**

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (3.51 mg, 7.5 µmol), $P(4\text{-}(F)C_6H_4)_3$ (7.11 mg, 22.5 µmol), $2\text{-}NO_2C_6H_4CO_2H$ (25.1 mg, 0.15 mmol) and indole ***trans*-202b** (36.1 mg, 0.10 mmol). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged anhydrous PhCN (1.0 mL). The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The reaction mixture was heated at 140 °C under a CO atmosphere for 72 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (10–20% EtOAc/pentane) to yield the title compound **205b** (5.51 mg, 14%) as a colourless oil; ν_{max}/ cm^{-1}: 2955 (m), 1634 (br. s), 1504 (s), 1465 (s), 1386 (s), 1252 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (1H, dd *J* = 8.0, 1.0 Hz, C**4**-H), 7.44 – 7.31 (m, 8H, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 5.81 (1H, s, C**10**-H), 5.19 (1H, d, *J* = 14.0 Hz, 1 × C1**4**-H_2), 4.66 (d, *J* = 14.0 Hz, 1 × C1**4**-H_2), 3.83 (3H, s, C**23**-H_3), 3.44 (1H, dd, *J* = 12.5, 1.0 Hz, 1 × C**12**-H_2), 2.85 (d, *J* = 12.5 Hz, 1 × C**12**-H_2), 2.01 (2H, td, *J* = 7.5, 1.0 Hz, C**19**-H_2), 1.36 – 1.23 (2H, m, C**20**-H_2), 1.18 – 1.05 (2H, m, C**21**-H_2), 0.79 (3H, t, *J* = 7.5, C**22**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9 (C**13**), 161.9 (C**9**), 140.4 (C**11**), 137.6, 137.5 (C**1** and C**8**), 136.1 (C**15**), 129.0, 128.9, 128.2 (C**16**, C**17** and C**18**), 125.2 (C**3**), 124.8 (C**6**), 123.4, 123.3, 123.3 (C**4**, C**5** and C**10**), 112.3 (**C2**), 109.8 (C**7**), 51.4 (C**14**), 45.9 (C**12**), 33.7 (C**19**), 32.2 (C**23**), 29.1 (C**20**), 22.2 (C**21**), 13.8 (C**22**); HRMS: (ESI)$^+$ Calculated for $C_{25}H_{27}N_2O_2$: 387.2067. Found [M + H]$^+$: 387.2076.

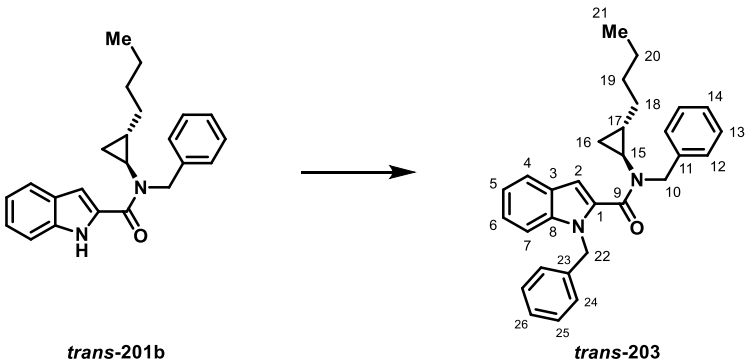
2-Benzyl-4-butyl-11-methyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (208b) and **(*Z*)-2-Benzyl-4-butyl-11-methyl-2,5-dihydro-1H-azocino[3,4-*b*]indole-1,6(11*H*)-dione (205b)**



General Procedure F: Indole ***trans*-202b** (36.1 mg, 0.10 mmol), fumaric acid (11.6 mg, 0.10 mmol) and anhydrous benzonitrile (0.10 mL) were employed, the reaction mixture was heated at 140 °C for 120 hours. The crude mixture was purified by flash column chromatography (10–15 % Et_2O/toluene) to yield the title compound **205b** and the title compound **208b** (18.8 mg, 50%). The major product **208b** was isolated as a colourless oil. The minor product **205b** was isolated as a colourless oil. *The spectroscopic properties of **205b** was consistent with the data previously reported in this thesis*.

Data for major compound **205b**: ν_{max}/ cm^{-1}: 2924 (m), 1633 (br. s), 1505 (s), 1466 (s), 1389 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, *J* = 7.5, 1.0 Hz, C**4**-H), 7.45 – 7.28 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H, and C**18**-H), 5.43 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 4.36 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.90 (3H, s, C**23**-H_3), 3.53 (1H, m, 1 × C**10**-H_2), 3.25 (1H, dd, *J* = 14.5, 5.0 Hz, 1 × C**10**-H_2), 3.09 (1H, dd, *J* = 13.0, 4.5 Hz, 1 × C**12**-H_2), 2.56 (1H, dd, *J* = 13.0, 4.0 Hz, 1 × C**12**-H_2), 2.18 (1H, m, C**11**-H), 1.44 – 1.03 (6H, m, C**19**-H_2, C**20**-H_2 and C**21**-H_2), 0.87 (3H, t, *J* = 7.0 Hz, C**22**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.1 (C**13**), 163.6 (C**9**), 137.7 (C**8**), 136.8, 136.7 (C**1** and C**15**), 129.1, 128.3, 128.2 (C**16**, C**17** and C**18**), 125.4 (C**3**), 125.0 (C**6**), 124.1 (C**4**), 123.7 (C**5**), 117.9 (C**2**), 110.0 (C**7**), 51.4 (C**10**), 48.7 (C**14**), 42.3 (C**12**), 36.5 (C**11**), 32.3 (C**23**), 30.5 (C**19**), 29.4 (C**20**), 22.7 (C**21**), 14.1 (C**22**); HRMS: $(ESI)^+$ Calculated for $C_{25}H_{28}N_2O_2$: 389.2224. Found $[M + H]^+$: 389.2224.

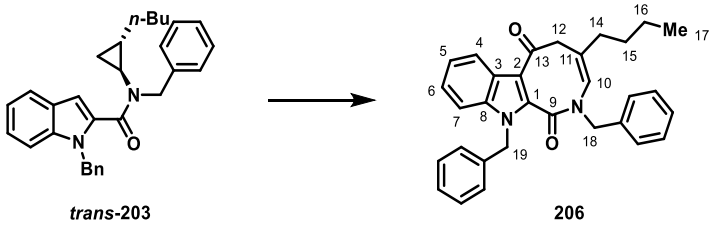
***N*,1-Dibenzyl-*N*-((1*S**,2*S**)-2-butylcyclopropyl)-1*H*-indole-2-carboxamide (*trans*-203)**



To a suspension of NaH (14 mg, 0.35 mmol, 60% dispersion in oil) in DMF (3 mL) at 0 °C was added amide ***trans*-201b** (100 mg, 0.29 mmol). After 15 minutes, benzyl bromide (55 mg, 0.32 mmol) was

added in one portion. The solution was then allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (15 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (15mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (20% EtOAc/hexane) to give the title compound ***trans*-203** (75 mg, 60%) as a yellow oil; ν_{max}/ cm^{-1}: 2922 (m), 1630 (s), 1526 (s), 1453 (s), 1419 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.42 (1H, m, C**7**-H), 7.35 – 7.06 (12H, m, C**5**-H, C**6**-H, 2 × C**12**-H, 2 × C**13**-H, C**14**-H, 2 × C**24**-H, 2 × C**25**-H and C**26**-H), 6.81 (1H, s, C**2**-H), 5.65 (2H, s, C**22**-H_2), 4.72 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 4.69 (1H, d, *J* = 14.5Hz, 1 × C**10**-H_2), 2.41 (m, 1H, C**15**-H), 1.17 – 1.00 (m, 5H, C**17**-H, C**18**-H_2 and C**19**-H_2), 0.78 – 0.71 (4H, m, 1 × C**20**-H_2 and C**21**-H_3), 0.56 (1H, m, 1 × C**20**-H_2), 0.41 – 0.30 (2H, m, C**16**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.9 (C**9**), 138.5, 138.0, 137.9 (C**8**, C**11**, C**23**), 132.4 (C**1**), 128.7, 128.5, 127.8, 127.5, 127.3, 127.2 (C**12**, C**13**, C**14**, C**24**, C**25** and C**26)**, 126.6 (C**3**), 123.8 (C**6**), 121.8 (C**4**), 120.4 (C**5**), 110.4 (C**7**), 106.1 (C**2**), 51.2 (C**10**), 47.5 (C**22**), 38.1 (C**15**), 31.7 (C**18**), 30.8 (C**19**), 22.8 (C**17**), 22.4 (C**20**), 15.9 (C**16**), 14.0 (C**21**); HRMS: $(ESI)^+$ Calculated for $C_{30}H_{33}N_2O$: 437.2587. Found $[M + H]^+$: 437.2580.

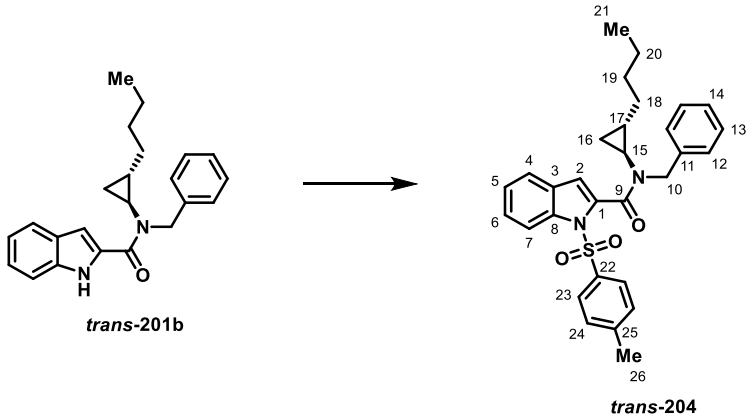
(*Z*)-2,11-Dibenzyl-4-butyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (206)



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (2.63 mg, 5.63 μmol), $P(4\text{-}(F)C_6H_4)_3$ (5.33 mg, 16.8 μmol), $2\text{-}NO_2C_6H_4CO_2H$ (18.8 mg, 0.113 mmol) and indole ***trans*-203** (33.1 mg, 0.075 mmol). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged anhydrous PhCN (1.0 mL). The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The reaction mixture was heated at 140 °C under a CO atmosphere for 72 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10–20% EtOAc/pentane) to yield the title compound **206** (5.51 mg, 9%) as a yellow oil; ν_{max}/ cm^{-1}: 3010 (m), 2956 (m), 1634 (br. s), 1506 (s), 1496 (s), 1453 (s), 1253 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 – 8.40 (1H, m, C**4**-H), 7.40 – 7.16 (13H, m, C**5**-H, C**6**-H, C**7**-H and 10 × ArC-H), 5.55 (2H, m, C**19**-H_2), 5.43 (1H, s, C**10**-H), 5.04 (1H, d, *J* = 14.0 Hz, 1 × C**18**-H_2), 4.22 (1H, d, *J* = 14.0 Hz, 1 × C**18**-H_2), 3.42 (1H, d, *J* = 13.0 Hz, 1 × C**12**-H_2), 2.83 (1H, d, *J* = 13.0 Hz, 1 × C**12**-H_2), 2.00 – 1.94 (2H, m, C**14**-H_2), 1.31 – 1.21 (2H, m, C**15**-H_2), 1.07 – 1.00 (2H, m, C**16**-H_2), 0.74 (3H, t, *J* = 7.5 Hz, C**17**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2 (C**13**), 161.9 (C**9**), 140.4 (C**11**), 137.3

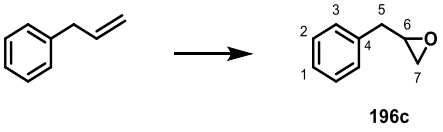
(ArC), 137.2 (ArC), 137.1 (ArC), 135.6 (ArC), 129.2, 128.8, 128.7, 128.6 (4 × Ar-CH), 128.5, 127.9 (2 × Ar-CH), 126.7, 126.6 (C**3** and C**6**) 123.2, 123.1, 123.0 (C**4**, C**5** and C**10**), 112.8 (C**2**), 104.6 (C**7**), 51.0 (C**18**), 48.1 (C**19**), 46.0 (C**12**), 33.6 (C**14**), 28.9 (C**15**), 21.9 (C**16**), 13.6 (C**17**); HRMS: $(ESI)^+$ Calculated for $C_{31}H_{31}N_2O_2$: 463.2307. Found $[M + H]^+$: 463.2314.

_N_,1-Dibenzyl-_N_-((1_S_*,2_S_*)-2-butylcyclopropyl)-1_H_-indole-2-carboxamide (*trans*-204)



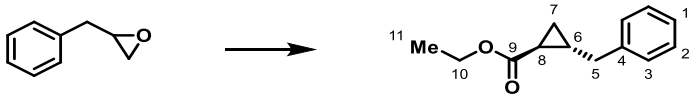
To a suspension of NaH (14 mg, 0.35 mmol, 60% dispersion in oil) in DMF (3 mL) at 0 °C was added indole ***trans*-201b** (100 mg, 0.29 mmol). After 15 minutes, *p*-toluenesulfonyl chloride (60 mg, 0.32 mmol) was added in one portion. The solution was then allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (15 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (5mL/mmol), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (5% Et_2O/toluene) to give the title compound ***trans*-204** (110 mg, 77%) as a yellow oil; ν_{max}/ cm^{-1}: 2925 (m), 1644 (s), 1449 (s), 1407 (s), 1371 (s), 1175 (s); ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 – 7.95 (3H, m, C**7**-H and 2 × C**23**-H), 7.49 (1H, dd, *J* = 8.0, 1.0 Hz, 1H, C**4**-H), 7.43 – 7.28 (6H, m, C**6**-H and 5 × Ar-CH), 7.22 (3H, m, C**5**-H and 2 × Ar-CH), 6.68 (1H, s, C**2**-H), 5.06 – 4.30 (2H, m, C**10**-H_2), 2.48 (1H, m, C**15**-H), 2.33 (3H, s, C**26**-H_3), 1.34 – 0.80 (8H, m, 1 × C**16**-H_2, C**17**-H, C**18**-H_2, C**19**-H_2, C**20**-H_2), 0.63 (3H, t, *J* = 7.0 Hz, C**21**-H_3), 0.33 (1H, dt, *J* = 7.0, 6.0 Hz, 1 × C**16**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.7 (C**9**), 145.1 (C**25**), 137.8 (C**22**), 135.5 (C**1**), 135.2 (C**8**), 134.8 (C**11**), 129.6 (Ar-CH), 129.3 (C**3**), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.9 (Ar-CH), 127.2 (C**14**), 125.3 (C**6**), 123.8 (C**5**), 121.5 (C**4**), 114.4 (C**7**), 109.8 (C**2**), 50.9 (C**10**), 38.2 (C**15**), 31.5 (C**18**), 30.3 (C**19**), 22.2 (C**20**), 21.6 (C**26**), 14.8 (C**16**), 14.1 (C**17**), 13.7 (C**21**); HRMS: $(ESI)^+$ Calculated for $C_{30}H_{33}N_2O_3S$: 501.2206. Found $[M + H]^+$: 501.2195.

2-Benzyloxirane (196c)



To a solution of allylbenzene (10.0 mL, 150 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added 3-chlorobenzoic acid (22.2 g, 90 mmol, 70% w/w) portion-wise over 10 minutes. The solution was warmed to room temperature and stirred for 16 hours. Saturated aqueous $NaHCO_3$ (150 mL) and CH_2Cl_2 (150 mL) were added and the organic layer was separated. The organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 150 mL), water (150 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound **196c** (11.7 g, 97 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.23 (5H, m, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 3.17 (1H, dddd, *J* = 5.5, 5.5, 4.0, 2.5 Hz, C**6**-H), 2.94 (1H, dd, *J* = 14.5, 5.5 Hz, 1 × C**5**-H_2), 2.85 (1H, d, *J* = 14.5, 5.5 Hz, 1 × C**5**-H_2), 2.81 (1H, dd, *J* = 5.0, 4.0 Hz, 1 × C**7**-H_2), 2.56 (1H, dd, *J* = 5.0, 2.5 Hz, 1 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2 (C**4**), 129.0, 128.8, 126.7 (C**1**, C**2** and C**3**), 52.4 (C**6**), 46.8 (C**7**), 38.7 (C**3**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

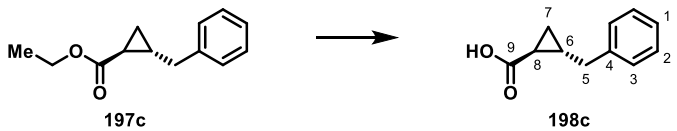
(1*S,2*R**)-Ethyl 2-benzylcyclopropane-1-carboxylate (197c**



196c 197c

To a solution of triethylphosphonoacetate (9.92 mL, 50.0 mmol) in anhydrous DME (100 mL) was added *n*-BuLi (20.0 mL, 50.0 mmol, 2.5 M in hexanes) dropwise over 15 minutes. The resulting solution was stirred at room temperature for 10 minutes, followed by the addition of 2-benzyloxirane **196c** (3.35 g, 25.0 mmol). The tube was sealed, and the reaction was stirred at 130 °C for 16 hours. The reaction was cooled to room temperature and saturated aqueous NH_4Cl (125 mL) was added. The solution was extracted with Et_2O (3 × 100 mL). The organic layers were combined, washed with H_2O (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacu*o. The residue was purified by flash column chromatography (5% EtOAc/petroleum ether) to afford the title compound **197c** (4.15 g, 80%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.20 (5H, m, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 4.12 (2H, q, *J* = 7.0 Hz, C**10**-H_2), 2.77 (1H, dd, *J* = 15.0, 6.5 Hz, 1 × C**5**-H_2), 2.58 (1H, dd, *J* = 15.0, 7.0 Hz, 1 × C**5**-H_2), 1.70 (1H, m, C**6**-H), 1.52 (1H, m, C**8**-H), 1.30 – 1.20 (4H, m, 1 × C**7**-H and C**11**-H_3), 0.83 (1H, m, 1 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C**9**), 140.1 (C**4**), 128.4 (2 signals) (C**2** and C**3**), 126.2 (C**1**), 60.4 (C**10**), 38.5 (C**5**), 23.0 (C**6**), 20.2 (C**8**), 15.2 (C**11**), 14.3 (C**7**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

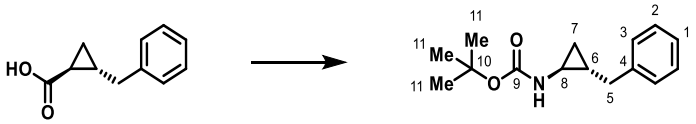
(1*S,2*R**)-2-Benzylcyclopropane-1-carboxylic acid (198c)**



197c 198c

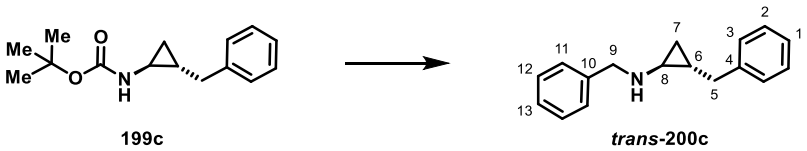
General Procedure D: Ester **197c** (4.51 g, 20.3 mmol) was employed to yield the title carboxylic acid **198c** (3.38 g, 95%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.20 (5H, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 2.73 (1H, dd, *J* = 15.0, 6.5 Hz, 1 × C**5**-H_2), 2.64 (1H, dd, *J* = 15.0, 7.0 Hz, 1 × C**5**-H_2), 1.76 (1H, m, C**6**-H), 1.54 (1H, m, C**8**-H), 1.31 (1H, ddd, *J* = 9.0, 4.5, 4.5 Hz, 1 × C**7**-H_2), 0.92 (1H, ddd, *J* = 8.0, 6.5, 4.5 Hz, 1 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.7 (C**9**), 140.0 (C**4**), 128.6, 128.5, 126.5 (C**1**, C**2** and C**3**), 38.5 (C**5**). 24.2 (C**6**), 20.2 (C**8**), 16.1 (C**7**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

(1*S,2*S**)-tert-Butyl (2-benzylcyclopropyl)carbamate (199c)**



To a solution of (1*S**,2*R**)-2-benzylcyclopropane-1-carboxylic acid **198c** (3.28 g, 18.6 mmol) and Et_3N (2.85 mL, 20.5 mmol) in *t*-BuOH (20 mL) was added diphenylphosphoryl azide (4.42 mL, 20.5 mmol) dropwise over 10 minutes. The reaction mixture was heated to 80 °C and stirred for 16 hours before cooling to room temperature and concentrating *in vacuo*. Saturated aqueous $NaHCO_3$ (150 mL) was added and the solution was extracted with Et_2O (3 × 75 mL). The organic extracts were combined, washed with water (75 mL) and brine (75 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (3% EtOAc/toluene) to afford the title compound **199c** (2.53 g, 55%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.15 (5H, m, C**1**-H, 2 × C**2**-H and 2 × C**3**-H), 4.68 (1H, br. s, NH), 2.84 (1H, dd, *J* = 14.5, 6.0 Hz, 1 × C**5**-H_2), 2.44 (2H, m, 1 × C**5**-H_2, C**8**-H), 1.45 (9H, s, 3 × C**11**-H_3), 1.15 (1H, ddddd, *J* = 9.0, 7.5, 6.0, 6.0, 3.0 Hz, C**6**-H), 0.84 – 0.57 (2H, m, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.6 (C**9**), 141.0 (C**4**), 128.5, 128.5 (2 signals), 126.2 (C**1**, C**2** and C**3**), 79.5 (C**10**), 38.1 (C**5**), 29.6 (C**8**), 28.5 (C**11**), 21.5 (C**6**), 14.03 (C**7**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

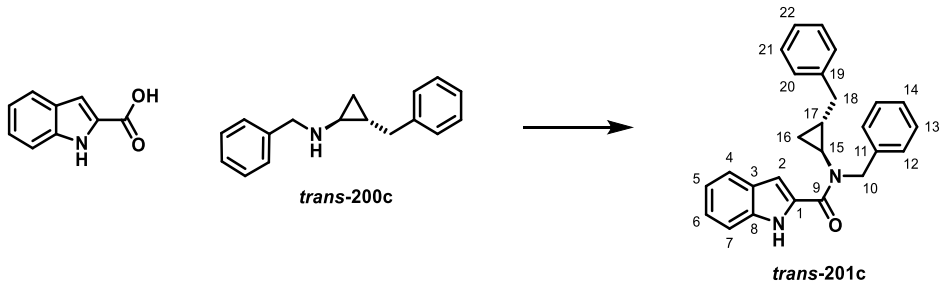
(1*S,2*S**)-*N*,2-Dibenzylcyclopropan-1-amine (*trans*-200c)**



General procedure E: Boc-protected amine **199c** (2.29 g, 9.27 mmol) was employed and the residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound ***trans*-200c** (1.83 g, 83%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.12 (10 H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H, 2 × C**11**-H, 2 × C1**2**-H and C1**3**-H), 3.72 (2H, s, C**9**-H_2), 2.53 (1H, dd, *J* = 15.0, 7.0 Hz, 1 × C**5**-H_2), 2.45 (1H, dd, *J* = 15.0, 7.5 Hz, 1 × C**5**-H_2), 2.02 (1H, ddd, *J* = 7.0, 3.5, 3.5 Hz, C**8**-H),

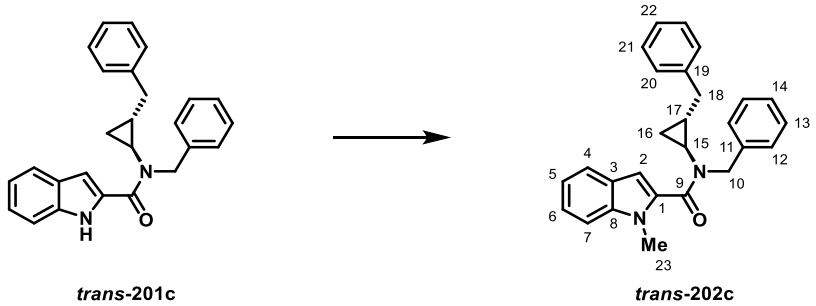
1.75 (1H, br. s, NH), 1.06 (1H, m, C**6**-H), 0.64 (1H, ddd, *J* = 8.5, 5.0, 3.5 Hz, 1 × C**7**-H_2), 0.41 (1H, ddd, *J* = 7.0, 5.0, 5.0 Hz, 1 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.8 (C**4**), 140.6 (C**10**), 128.5 (2 signals), 128.4, 128.3, 127.0, 126.0 (C**1**, C**2**, C**3**, C**11**, C**12** and C**13**), 53.8 (C**9**), 38.5 (C**5**), 37.4 (C**8**), 21.7 (C**6**), 14.0 (C**7**). *The spectroscopic properties of this compound were consistent with the data available in the literature.*[16]

_N_-Benzyl-_N_-((1_S_*, 2_S_*)-2-benzylcyclopropyl)-1_H_-indole-2-carboxamide (*trans*-201c)



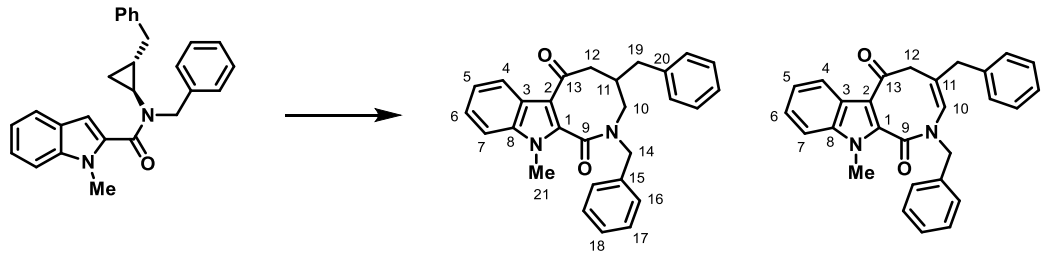
General Procedure B: 1*H*-Indole-2-carboxylic acid (570 mg, 3.53 mmol) and (1*S**,2*S**)-*N*,2-dibenzylcyclopropan-1-amine **(*trans*-200c)** (880 mg, 3.71 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (10% EtOAc/toluene) to give the title compound ***trans*-201c** (950 mg, 67%) as a colourless solid; m.p.: 172–173 °C (ethanol); ν_{max}/ cm^{-1}: 3275 (br. m), 1605 (s), 1520 (s), 1436 (s), 1402 (s), 1312 (m), 1279 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (1H, br. s, NH), 7.66 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.41 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H), 7.33 – 7.19 (7H, m, 7 × ArC-H), 7.17 – 7.05 (6H, m, 7 × ArC-H), 4.95 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.61 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 2.89 (1H, ddd, *J* = 7.0, 4.0, 3.5 Hz, C**15**-H), 2.71 (1H, m, 1 × C**18**-H_2), 2.48 (1H, dd, *J* = 14.5, 7.5 Hz, 1 × C**18**-H_2), 1.45 (1H, m, C**17**-H), 1.03 (1H, ddd, *J* = 9.5, 6.0, 4.0 Hz, 1 × C**16**-H_2), 0.95 (1H, m, 1 × C**16**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.8 (C**9**), 140.2 (C**19**), 138.0 (C**11**), 135.8 (C**8**), 130.2 (C**1**), 128.7, 128.6, 128.6, 127.9, 127.6, 127.3, 126.5 (C**3**, C**12**, C**13**, C**14**, C**20**, C**21** and C**22**), 124.7 (C**6**), 122.2 (C**4**), 120.5 (C**5**), 111.9 (C**7**), 107.1 (C**2**), 52.0 (C**10**), 38.2 (C**15**), 37.8 (C**18**), 23.9 (C**17**), 18.5 (C**16**); HRMS: $(ESI)^+$ Calculated for $C_{26}H_{25}N_2O$: 381.1961. Found $[M + H]^+$: 381.1972.

_N_-Benzyl-_N_-((1_S_*, 2_S_*)-2-benzylcyclopropyl)-1-methyl-1_H_-indole-2-carboxamide (*trans*-202c)



To a suspension of NaH (74 mg, 3.10 mmol, 60% dispersion in oil) in DMF (5 mL) at 0 °C was added *N*-benzyl-*N*-((1*S**,2*S**)-2-benzylcyclopropyl)-1*H*-indole-2-carboxamide (***trans*-201c)** (590 mg, 1.55 mmol). After 15 minutes, iodomethane (0.11 mL, 1.71 mmol) was added dropwise over 10 minutes. The solution was warmed to room temperature and stirred for 4 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (50 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30-50% Et_2O/hexane) to give the title compound ***trans*-202c** (500 mg, 81%) as a yellow oil; ν_{max}/ cm^{-1}: 3027 (m), 1631 (s), 1464 (m), 1453 (s), 1403 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.40 – 7.24 (5H, m, 5 × Ar-CH), 7.23 – 7.09 (6H, m, 6 × Ar-CH), 6.92 – 6.91 (2H, m, 2 × Ar-CH), 6.74 (1H, s, C**2**-H), 4.70 (2H, s, C**10**-H_2), 3.83 (3H, s, C**23**-H_3), 2.60 (1H, dd, *J* = 7.5, 3.5 Hz, C**15**-H), 2.49 (1H, m, 1 × C**18**-H_2), 2.13 (1H, m, 1 × C**18**-H_2), 1.18 (1H, m, C**17**-H), 0.82 – 0.55 (2H, m, C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1 (C**9**), 140.2 (C**19**), 138.1 (C**8**), 137.7 (C**11**), 133.1 (C**1**), 128.7, 128.5, 127.9, 127.5, 126.7, 126.3 (C**3**, C**12**, C**13**, C**14**, C**20**, C**21** and C**22**), 123.5 (C**6**), 121.7 (C**4**), 120.3 (C**5**), 109.9 (C**7**), 104.4 (C**2**), 51.3 (C**10**), 37.7 (C**18**), 37.5 (C**15**), 31.3 (C**23**), 24.2 (C**17**), 16.3 (C**16**); HRMS: $(ESI)^+$ Calculated for $C_{27}H_{27}N_2O$: 395.2118. Found $[M + H]^+$: 395.2119.

2,4-Dibenzyl-11-methyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (*rac*-205c) and **(*Z*)-2,4-Dibenzyl-11-methyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (208c)**



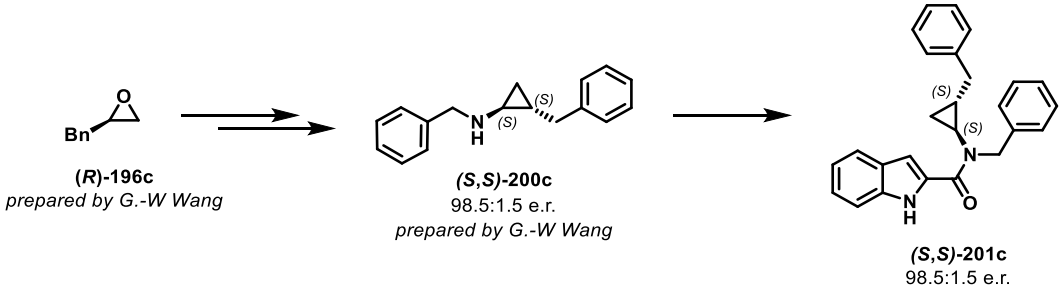
General Procedure F: Compound ***trans*-202c** (39.4 mg, 0.10 mmol), fumaric acid (17.6 mg, 0.15 mmol) and anhydrous benzonitrile (0.15 mL) were employed, the reaction mixture was heated at 140 °C for 72 hours. The crude mixture was purified by flash column chromatography (10% toluene/hexane) to yield the title compound ***rac*-205b** and the title compound **208b** (21.2 mg, 50%). ^1H NMR analysis revealed a 14:1 ratio of ***rac*-205b**:**208b**. The major product ***rac*-205b** was isolated as a colourless solid.

Data for major compound ***rac*-205b**: m.p.: 79–81 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 2924 (m), 1682 (s), 1630 (s), 1466 (s), 1417 (s), 1266 (s); ^1H NMR (500 MHz, CD_3CN, 65 °C): δ 7.88 (1H, d, *J* = 7.5 Hz, Ar-CH), 7.56 (1H, m, Ar-CH), 7.49 (1H, m, Ar-CH), 7.43 (1H, m, Ar-CH), 7.38 – 7.32 (2H, m, 2, Ar-CH), 7.31 – 7.24 (6H, m, 6 × Ar-CH), 7.10 (1H, m, Ar-CH), 6.63 (1H, m, Ar-CH), 4.83 (2H, s, C**14**-H_2), 3.78 (3H, s, C**21**-H_3), 3.68 – 3.54 (2H, m, C**10**-H_2), 3.04 (1H, d, *J* = 15.5 Hz, 1 × C**19**-H_2), 2.76 – 2.66 (3H, br.

m, C**11**-H, 1 × C**12**-H_2 and 1 × C**19**-H_2), 2.36 (1H, br. m, 1 × C**12**-H_2); ^{13}C NMR (126 MHz, CD_3CN): δ 197.9 (C**13**, *A*+*B*), 166.1 (C**9**, *A*+*B*), 144.3, 144.0 (C**20**, *A*+*B*), 138.6, 138.4 (C**15** and C**8**, *A*+*B*), 134.6 (Ar-CH), 133.72 (Ar-C), 133.2 (Ar-C), 130.3, 129.7, 128.4, 128.0, 127.7, 127.5, 127.3 (6 × Ar-CH and 1 × Ar-C), 124.0 (Ar-CH), 122.3 (Ar-CH), 121.1 (Ar-CH), 111.0 (Ar-CH), 103.1 (Ar-CH), 54.0, 53.5 (C**14**, *A*+*B*), 49.6, 48.7 (C**19**, *A*+*B*), 43.4, 43.0 (C**12**, *A*+*B*), 34.6, 34.3, 33.8 (C**11**, C**19**, *A*+*B*), 31.7 (C**21**, *A*+*B*); HRMS: (ESI)$^+$ Calculated for $C_{28}H_{27}N_2O_2$: 423.2067. Found [M + H]$^+$: 423.2065. *A ^{1}H NMR spectrum was recorded at 65 °C in* CD_3CN *because at room temperature slow conformational interconversion gave a broad spectrum. Due to the presence of rotamers and line broadening, it was not possible to confidently assign aromatic signals.*

Data for minor compound **208b**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (1H, s, C**10**-H). *The minor product was tentatively assigned by analogy to that of minor product of* **208a**.

***N*-Benzyl-*N*-((1*S*, 2*S*)-2-benzylcyclopropyl)-1*H*-indole-2-carboxamide (*enantiopure*)**



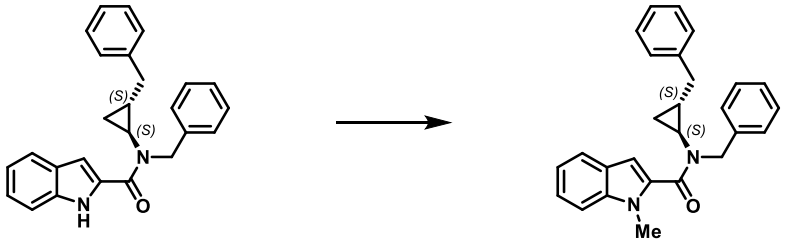
Enantioenriched **(*R*)-196c** (>99:1 e.r.) was prepared by G.-W. Wang according to a procedure reported by Jacobsen and co-workers.[165] **(*R*)-196c** was then employed in the same cyclopropanation, hydrolysis, *N*-Boc deprotection/benzylation and amide coupling sequence as described above for the racemate to access enantiopure (*N*-Benzyl-*N*-((1*S*, 2*S*)-2-benzylcyclopropyl)-1*H*-indole-2-carboxamide **(**98.5:1.5 e.r.). *(1S, 2S)-N,2-dibenzylcyclopropan-1-amine **(S,S)-200c** was prepared by G.-W. Wang.*

General Procedure B: 1*H*-Indole-2-carboxylic acid (242 mg, 1.50 mmol) and (1*S*, 2*S*)-*N*,2-dibenzylcyclopropan-1-amine (356 mg, 1.50 mmol) were employed and the reaction was stirred at r.t. for 18 hours. The crude residue was purified by flash column chromatography (10–15% Et_2O/toluene) to give the title compound **(*S*,*S*)-200c** (541 mg, 95%) as a colourless solid.

The enantiopurity of this compound was confirmed after the subsequent step.

$[\alpha]_D^{19}$ +28.20 (c = 0.69, $CHCl_3$). *All other analytical data were identical to those reported earlier.*

***N*-Benzyl-*N*-((1*S*, 2*S*)-2-benzylcyclopropyl)-1-methyl-1*H*-indole-2-carboxamide ((*S*,*S*)-202c)**



***(S,S)*-201c**
98.5:1.5 e.r.

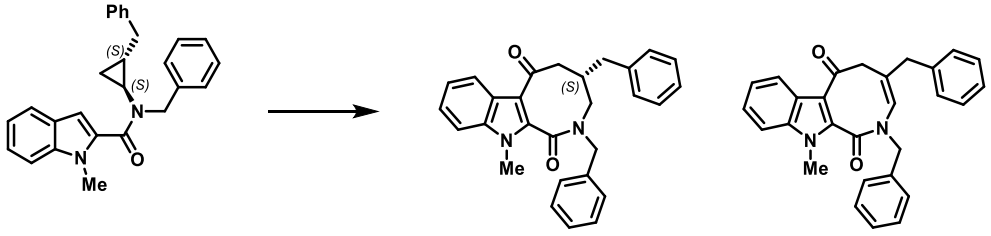
***(S,S)*-202c**
98.5:1.5 e.r.

To a suspension of NaH (73 mg, 3.02 mmol, 60% dispersion in oil) in DMF (5 mL) at 0 °C was added *N*-benzyl-*N*-((1*S*, 2*S*)-2-benzylcyclopropyl)-1*H*-indole-2-carboxamide (*enantiopure*) (150 mg, 0.39 mmol). After 15 minutes, iodomethane (0.03 mL, 0.43 mmol) was added in over 5 minutes. The solution was then warmed to room temperature and stirred for 4 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (25% EtOAc/hexane) to give the title compound **(*S*,*S*)-202c** (138 mg, 91%) as a yellow oil.

The enantiopurity of this compound was confirmed after the subsequent step.

$[\alpha]_D^{19}$ +19.51 (c = 4.66, $CHCl_3$). *All other analytical data were identical to those reported earlier.*

(*S*)-2,4-Dibenzyl-11-methyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione ((S)-205c) and **(*Z*)-2,4-Dibenzyl-11-methyl-2,5-dihydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (208b)**



***(S,S)*-202c**

***(S)*-208c**

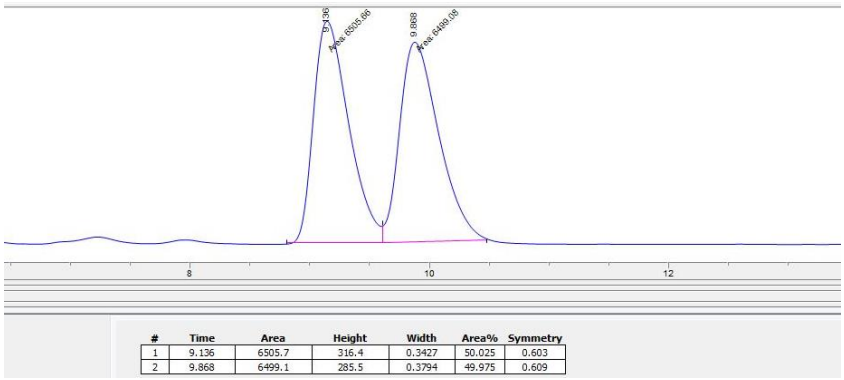
205c

14:1
***(S)*-205c:208c**

<u>General Procedure F:</u> Compound **(*S*,*S*)-202c** (39.4 mg, 0.10 mmol), fumaric acid (17.6 mg, 0.15 mmol) and anhydrous benzonitrile (0.15 mL) were employed, the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (10 % toluene/hexane) to yield the title compound **(*S*)-205c** and compound **208c** (21.0 mg, 50%). ^{1}H NMR analysis revealed a 14:1 ratio of **(*S*)-208c**:**205c**.

$[\alpha]_D^{23}$ +42.16 (c = 0.90, $CHCl_3$). *All other analytical data were identical to those reported earlier.*

The enantiopurity of this compound was determined by chiral SFC (Chiralpak IA, isocratic CO_2-MeOH 65:35, 2.0 mL/min, 25 ^oC) against a racemic standard; (t_R major – 9.14 min and t_R (minor) – 9.87 min).



#	Time	Area	Height	Width	Area%	Symmetry
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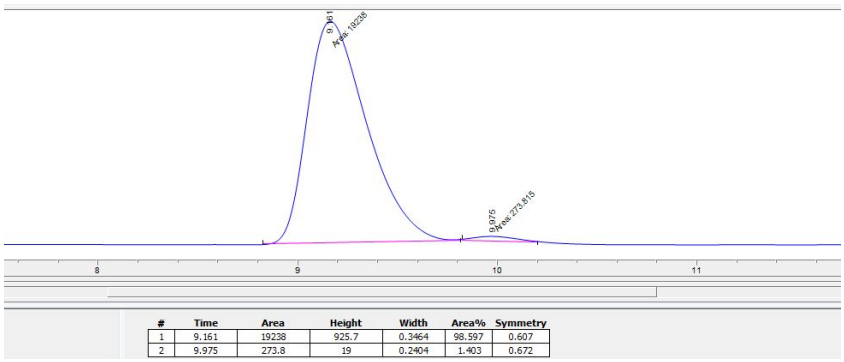
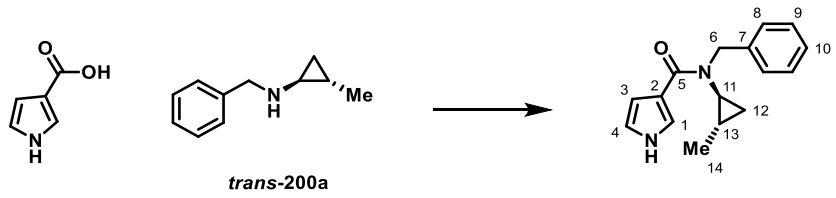
2	9.868	6499.1	285.5	0.3794	49.975	0.609



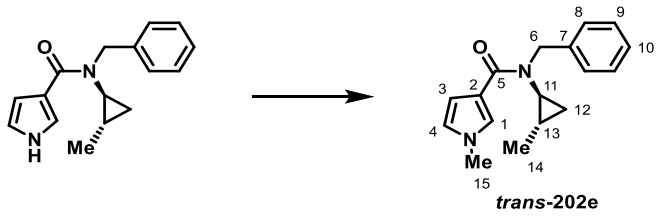
#	Time	Area	Height	Width	Area%	Symmetry
1	9.161	19238	925.7	0.3464	98.597	0.607
2	9.975	273.8	19	0.2404	1.403	0.672

***N*-Benzyl-*N*-((1*S**,2*S**)-2-methylcyclopropyl)-1*H*-pyrrole-3-carboxamide**



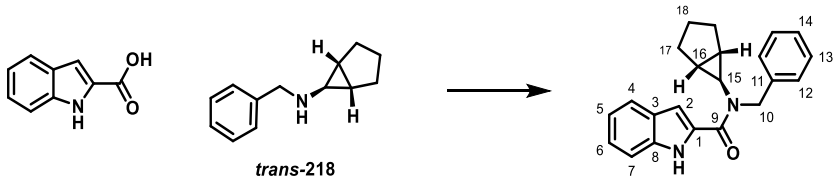
General Procedure B: 1*H*-Indole-2-carboxylic acid (244 mg, 2.19 mmol) and (1*S**, 2*S**)-*N*-benzyl-2-methylcyclopropan-1-amine ***trans*-200a** (372 mg, 2.31 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (60% EtOAc/toluene) to give the title compound (403 mg, 72%) as a yellow oil; ν_{max}/ cm^{-1}: 3673 (m), 2956 (m), 1716 (s), 1593 (s), 1416 (s), 1310 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, br. s, NH), 7.36 – 7.22 (6H, m, C**1**-H, 2 × C**8**-H, 2 × C**9**-H, and C**10**-H), 6.72 (1H, dd, *J* = 2.5, 2.5 Hz, C**4**-H), 6.58 (1H, d, *J* = 2.5 Hz, C**3**-H), 4.79 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H_2), 4.72 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H_2), 2.42 (1H, ddd, *J* = 7.0, 3.5, 3.5 Hz, C**11**-H), 0.98 (1H, m, C**13**-H), 0.91 (3H, d, *J* = 6.0 Hz, C**14**-H_3), 0.79 (1H, m, 1 × C**12**-H_2), 0.48 (1H, m, 1 × C**12**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.7 (C**5**), 138.7 (C**7**), 128.6, 128.0, 127.1 (C**8**, C**9** and C**10**), 122.1 (C**1**), 120.2 (C**2**), 117.6 (C**4**), 110.1 (C**3**), 51.1 (C**6**), 38.7 (C**11**), 17.8 (2 signals) (C**12** and C**13**), 17.4 (C**14**); HRMS: $(ESI)^+$ Calculated for $C_{16}H_{19}N_2O$: 255.1492. Found $[M + H]^+$: 255.1494.

_N_-Benzyl-1-methyl-_N_-((1_R_*, 2_R_*)-2-methylcyclopropyl)-1_H_-pyrrole-3-carboxamide (*trans*-202e)



To a suspension of NaH (91.2 mg, 2.28 mmol, 60% dispersion in oil) in DMF (8.0 mL) at 0 °C was added *N*-benzyl-*N*-((1*R**,2*R**)-2-methylcyclopropyl)-1*H*-pyrrole-3-carboxamide (193 mg, 0.76 mmol). After 15 minutes, iodomethane (0.095 mL, 1.52 mmol) was added dropwise over 5 minutes. The solution warmed to room temperature and stirred for 6 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (15 mL) and extracted with EtOAc (3 × 15 mL). The organic extracts were combined, washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50% EtOAc/ hexane) to give the title compound ***trans*-202e** (170 mg, 83%) as a colourless solid; m.p.: 95–97 °C (EtOAc/ hexane); ν_{max}/ cm^{-1}: 2953 (m), 1605 (s), 1533 (s), 1411 (s), 1258 (s), 751 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.21 (5H, m, 2 × C**8**-H, 2 × C**9**-H, and C**10**-H), 7.14 (1H, s, C**1**-H), 6.70 – 6.31 (2H, m, C**3**-H and C**4**-H), 4.77 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H_2), 4.71 (1H, d, *J* = 15.0 Hz, 1 × C**6**-H_2), 3.65 (3H, s, C**15**-H_3), 2.40 (1H, m, C**11**-H), 0.99 (1H, m, C**13**-H), 0.92 (3H, d, *J* = 6.0 Hz, C**14**-H_3), 0.80 (1H, m, 1 × C**12**-H_2), 0.48 (1H, m, 1 × C**12**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$, 50 °C): δ 168.3 (C**5**), 140.0 (C**6**), 128.5, 128.0, 127.0 (C**8**, C**9** and C**10**), 125.9 (C**1**), 121.4 (C**4**), 120.3 (C**2**), 110.5 (C**3**), 51.2 (C**6**), 38.8 (C**11**), 36.4 (C**15**), 17.8, 17.7 (C**13** and C**12**), 17.4 (C**14**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{21}N_2O$: 269.1648. Found $[M + H]^+$: 269.1645.

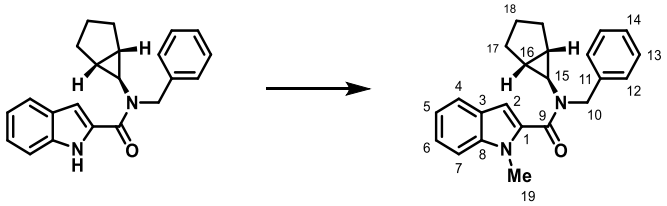
_N_-benzyl-_N_-((1_R_*,5_S_*,6_R_*)-bicyclo[3.1.0]hexan-6-yl)-1H-indole-2-carboxamide



General Procedure B: *Amine **trans-218** was synthesised by G.W.-Wang.* 1*H*-Indole-2-carboxylic acid (154 mg, 0.96 mmol) and (1*S**, 2*S**)-*N*-benzyl-2-methylcyclopropan-1-amine ***trans*-218** (180 mg, 0.96 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (10% Et_2O/toluene) to give the title compound (228 mg, 72%) as white solid; m.p.: 167–169 °C (EtOAc/ hexane); ν_{max}/ cm^{-1}: 3255 (br. m), 2944 (m), 1606 (s), 1522 (s), 14101 (s), 1277 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (1H, br. s, NH), 7.59 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.34 (1H, d, *J* = 8.5 Hz, C**7**-H), 7.29 – 7.19 (6H, m, C**6**-H, 2 × C**12**-H, 2 × C**13**-H, and C**14**-H), 7.09 – 6.96 (2H, m, C**2**-H and C**5**-H), 4.79 (2H, s, C**10**-H_2), 2.57 (1H, d, *J* = 2.0 Hz, C**15**-H), 1.81

(2H, dd, m, 2 × C**17**-H), 1.68 (2H, m, 2 × C**17**-H), 1.61 – 1.47 (3H, m, 2 × C**16**-H and 1 × C**18**-H), 1.04 (1H, dtt, *J* = 13.5, 11.0, 5.5 Hz, 1 × C**18**-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.6 (C**9**), 138.0 (C**11**), 135.7 (C**8**), 130.5 (C**1**), 128.7 (Ar-CH), 128.0 (2 signals, C**3** and Ar-CH), 127.4 (Ar-CH), 124.70 (C**6**), 122.3 (C**4**), 120.5 (C**7**), 111.9 (C**5**), 106.9 (C**2**), 51.5 (C**10**), 38.3 (C**15**), 29.2 (C**16**), 27.8 (C**17**), 21.7 (C**18**); HRMS: (ESI)$^+$ Calculated for $C_{22}H_{23}N_2O$: 331.1805. Found [M + H] $^+$: 331.1821.

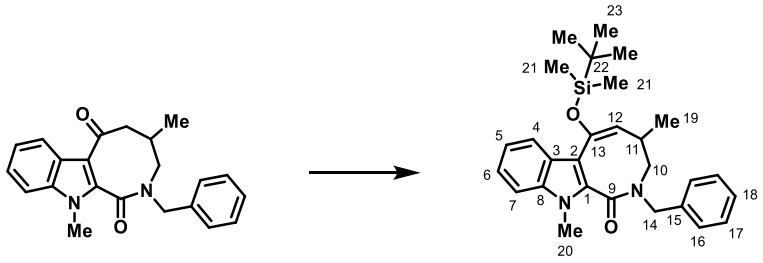
_N_-benzyl-_N_-((1_R_*,5_S_*,6_R_*)-bicyclo[3.1.0]hexan-6-yl)-1-methyl-1H-indole-2-carboxamide (*trans*-219)



***trans*-219**

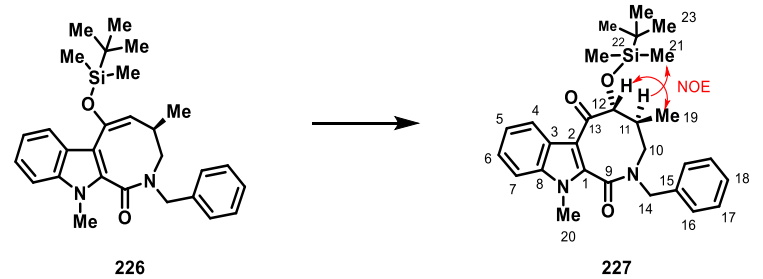
To a suspension of NaH (26.0 mg, 0.72 mmol, 60% dispersion in oil) in DMF (4.0 mL) at 0 °C was added *N*-benzyl-*N*-((1*R**,2*R**)-2-methylcyclopropyl)-1*H*-pyrrole-3-carboxamide (200 mg, 0.60 mmol). After 15 minutes, iodomethane (40.0 μL, 0.72 mmol) was added dropwise over 5 minutes. The solution warmed to room temperature and stirred for 6 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL) and extracted with EtOAc (3 × 15 mL). The organic extracts were combined, washed with H_2O (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50% EtOAc/ hexane) to give the title compound ***trans*-219** (170 mg, 83%) as a colourless solid; m.p.: 95–97 °C (EtOAc/ hexane); ν_{max}/ cm^{-1}: 2926 (m), 1627 (s), 1519 (s), 1402 (s), 1313 (s); ^{1}H NMR (400 MHz, $CDCl_3$): 7.63 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.42 – 7.28 (7H, m, C**6**-H, C**7**-H, 2 × C**12**-H, 2 × C**13**-H, and C**14**-H,), 7.14 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-H), 6.76 (1H, s, C**2**-H), 4.79 (2H, s, C**10**-H_2), 3.90 (3H, s, C**19**-H_3), 2.40 (1H, t, *J* = 2.0 Hz, C**15**-H), 1.68 – 1.41 (7H, m, 2 × C**16**-H_2, 2 × C**17**-H_2 and 1 × C**18**-H), 0.92 (1H, m, 1 × C**18**-H);^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8 (C**9**), 138.1 (C**8**), 137.7 (C**11**), 133.1 (C**1**), 128.7, 128.2, 127.6 (C**12**, C**13** and C**14**), 126.6 (C**3**), 123.4 (C**6**), 121.7 (C**4**), 120.1 (C**5**), 110.0 (C**7**), 104.7 (C**2**), 50.9 (C**10**), 38.5 (C**1**5), 31.5 (C**19**), 29.0 (C**16**), 27.3 (C**17**), 21.6 (C**18**); HRMS: (ESI)$^+$ Calculated for C23H24N_2NaO: 367.1781. Found [M + Na] $^+$: 367.1772.

(*E*)-2-Benzyl-6-((*tert*-butyldimethylsilyl)oxy)-4,11-dimethyl-2,3,4,11-tetrahydro-1*H*-azocino[3,4-*b*]indol-1-one (226)



To a stirred solution of **208a** (49.8 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C was added Et_3N (32.0 uL, 0.23 mmol) dropwise under argon. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (46.3 uL, 0.20 mmol) was then added and the mixture was slowly warmed to room temperature and stirred for 6 hours. Then the mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10% EtOAc/Hex) to yield (*E*)-2-benzyl-6-((tert-butyldimethylsilyl)oxy)-4,11-dimethyl-2,3,4,11-tetrahydro-1*H*-azocino[3,4-*b*]indol-1-one (59.0 mg, 89%) as a colourless oil; ν_{max}/ cm^{-1}: 2928 (m), 1639 (s), 1472 (m), 1252 (m), 1154 (s), 832 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.43 – 7.27 (7H, m, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H, and C**18**-H), 7.15 (1H, m, C**5**-H), 5.17 (1H, d, *J* = 6.0 Hz, C**12**-H), 5.06 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 4.61 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.90 – 3.78 (4H, m, 1 × C**10**-H_2 and C**20**-H_3), 2.94 (1H, dd, *J* = 14.5, 5.0 Hz, 1 × C**10**-H_2), 2.59 (1H, m, C**11**-H), 0.90 (3H, d, *J* = 6.8 Hz, C**19**-H_3), 0.85 (9H, s, 3 × C**23**-H_3), -0.04 (3H, s, 1 × C**21**-H_3), -0.29 (3H, s, 1 × C**21**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.6 (C**9**), 143.5 (C**13**), 138.1 (C**8**), 137.6 (C**15**), 129.1 (C**1**), 128.8, 128.3, 127.7 (C**16**, C**17** and C**18**), 126.3 (C**3**), 123.7 (C**6**), 123.3 (C**4**), 120.2 (C**5**), 114.4 (C**2**), 113.8 (C**12**), 109.7 (C**7**), 53.7 (C**10**), 49.3 (C**14**), 32.0 (C**11**), 31.2 (C**20**), 25.9 (C**23**), 20.1 (C**19**), 18.4 (C**22**), -4.8 (C**21**), -4.9 (C**21**); HRMS: $(ESI)^+$ Calculated for $C_{28}H_{37}N_2O_2Si$: 461.2619. Found $[M + H]^+$: 461.2626.

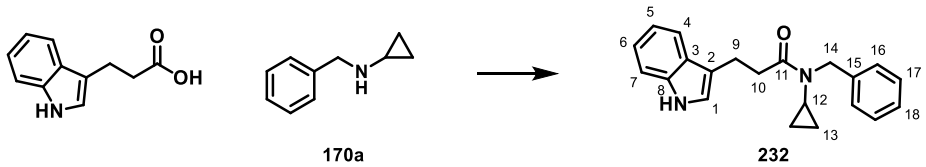
(4*S,5*R**)-2-Benzyl-5-((*tert*-butyldimethylsilyl)oxy)-4,11-dimethyl-2,3,4,5-tetrahydro-1*H*-azocino[3,4-*b*]indole-1,6(11*H*)-dione (227)**



To a stirred solution of (*E*)-2-Benzyl-6-((tert-butyldimethylsilyl)oxy)-4,11-dimethyl-2,3,4,11-tetrahydro-1*H*-azocino[3,4-*b*]indol-1-one **226** (31.1 mg, 0.068 mmol) in anhydrous CH_2Cl_2 (1.00 mL)

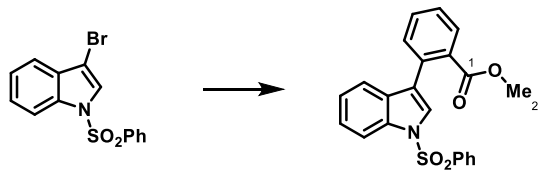
at -78 °C was added 3-chloroperbenzoic acid (*m*-CPBA) (26.3 mg, 0.11 mmol) in CH_2Cl_2 (0.75 mL) dropwise under an atmosphere of argon. The mixture was slowly warmed to room temperature and stirred for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (3% EtOAc/toluene) to afford the title compound **227** (22.4 mg, 70%) as a colourless oil as a single diastereomer. *The relative stereochemistry of **227** was corroborated by nOe experiments (as indicated on the compound structure **227**). nOe correlations were observed between C**12**-H and C**19**-H, and from C**11**-H to C**15**-H.* ν_{max}/ cm^{-1}: 2927 (m), 1638 (s), 1504 (s), 1466 (s), 1380 (s), 1054 (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.45 – 7.31 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H, and C**18**-H), 5.54 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 4.87 (1H, d, *J* = 5.0 Hz, C**12**-H), 4.31 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.91 (3H, s, C**20**-H_3), 3.55 (1H, dd, *J* = 15.0, 13.5 Hz, 1 × C**10**-H_2), 3.23 (1H, dd, *J* = 15.0, 5.5 Hz, 1 × C**10**-H_2), 2.50 (1H, m, C**11**-H), 0.93 (9H, s, 3 × C**23**-H_3), 0.84 (3H, d, *J* = 7.0 Hz, C**19**-H_3), 0.13 (3H, s, 1 × C**21**-H_3), 0.00 (3H, s, 1 × C**21**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.9 (C**13**), 163.3 (C**9**), 137.6 (C**8**), 136.5 (C**15**), 135.2 (C**1**), 129.2, 128.3, 128.2 (C**16**, C**17** and C**18**), 125.7 (C**3**), 125.1 (C**6**), 124.4 (C**4**), 123.8 (C**5**), 115.6 (C**2**), 110.0 (C**7**), 75.4 (C**12**), 51.2 (C**10**), 48.5 (C**14**), 38.9 (C**11**), 32.3 (C**20**), 26.1 (C**23**), 18.6 (C**22**), 11.3 (C**19**), -4.4 (C**21**), -5.2 (C**21**); HRMS: $(ESI)^+$ Calculated for $C_{28}H_{37}N_2O_3Si$: 477.2568. Found $[M + H]^+$: 477.2575.

***N*-Benzyl-*N*-cyclopropyl-3-(1*H*-indol-3-yl)propenamide (232)**



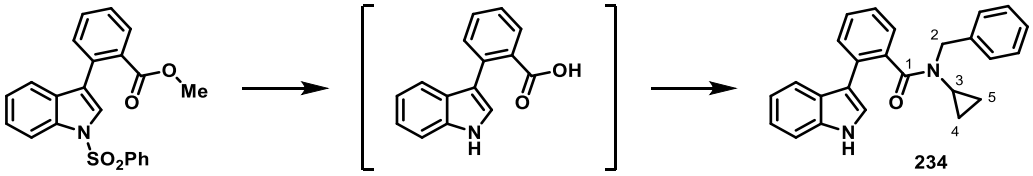
General Procedure B: 3-(1*H*-indol-3-yl)propanoic acid (278 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (308 mg, 2.10 mmol) were employed and the reaction was stirred at r.t. for 4 hours. The crude residue was purified by flash column chromatography (50% EtOAc/hexane) to give the title compound **232** (350 mg, 55%) as a colourless solid; m.p.: 141–143 °C (ethanol); ν_{max} / cm^{-1}: 3302 (br. s), 3032 (w), 1627 (s), 1440 (s), 1411 (s), 1223 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, br. s, NH), 7.65 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.36 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.32 – 7.07 (7H, m, C**5**-H, C**6**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.01 (1H, d, *J* = 2.5 Hz, C**1**-H), 4.61 (2H, s, C**14**-H_2), 3.19 (2H, t, *J* = 7.5 Hz, C**9**-H_2), 3.05 – 2.94 (2H, m, C**10**-H_2), 2.41 (1H, tt, *J* = 7.0, 4.0 Hz, C**12**-H), 0.81 – 0.64 (4H, m, 2 × C**13**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8 (C**11**), 138.5 (C**15**), 136.4 (C**8**), 128.5, 127.8 (C**16** and C**17**), 127.5 (C**3**), 127.0 (C**18**), 122.0, 121.9 (C**1** and C**6**), 119.4 (C**5**), 118.9 (C**4**), 115.8 (C**2**), 111.3 (C**7**), 49.9 (C**14**), 35.1 (C**10**), 30.1 (C**12**), 21.1 (C**9**), 9.4 (C**13**); HRMS: $(ESI)^+$ Calculated for $C_{21}H_{22}N_2NaO$: 341.1624. Found $[M + Na]^+$: 341.1637.

Methyl 2-(1-(phenylsulfonyl)-1H-indol-3-yl)benzoate



To an oven dried reaction tube was added 3-bromo-1-(phenylsulfonyl)-1H-indole (504 mg, 1.50 mmol), (2-(methoxycarbonyl)phenyl)boronic acid (403 mg, 2.25 mmol), $Pd(PPh_3)_4$ (87.0 mg, 0.075 mmol) and K_2CO_3 (518 mg, 3.75 mmol). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in 1,4-dioxane/H_2O (3:1, 6.5 mL) The tube was sealed and heated at 105 °C for 4 hours and then cooled to room temperature. The reaction mixture was filtered through a pad of celite® and concentrated *in vacuo.* The residue was purified by flash column chromatography (30% Et_2O/hexane) to afford the title compound (352 mg, 60%) as a colourless oil; ν_{max} / cm^{-1}: 2948 (m), 1721 (s), 1448 (s), 1368 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, dd, *J* = 8.5, 1.0 Hz, ArC-H), 7.94 – 7.88 (3H, m, 3 × ArC-H), 7.62 – 7.51 (3H, m, 3 × ArC-H), 7.49 – 7.41 (4H, m, 4 × ArC-H), 7.35 – 7.27 (2H, m, 2 × ArC-H), 7.20 (1H, dd, *J* = 8.0, 7.0, 1.0 Hz, ArC-H), 3.29 (3H, s, C**2**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6 (C**1**), 138.3 (ArC), 134.9 (Ar-CH), 133.9 (ArC), 132.6 (Ar-CH), 131.9 (Ar-CH), 131.6 (Ar-CH), 131.5 (Ar-CH), 130.7 (ArC), 130.4 (Ar-CH), 129.3 (Ar-CH), 128.1 (Ar-CH), 126.9 (Ar-CH), 125.0 (ArC), 124.1 (Ar-CH), 123.4 (Ar-CH), 123.7 (Ar-CH), 120.7 (ArC), 120.0 (Ar-CH), 115.0 (ArC), 113.9 (Ar-CH), 51.9 (C**2**); HRMS: $(ESI)^+$ Calculated for $C_{22}H_{18}NO_4S$: 391.0878. Found $[M + H]^+$: 391.0880.

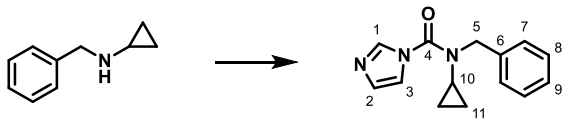
***N*-Benzyl-*N*-cyclopropyl-2-(1H-indol-3-yl)benzamide (234)**



To a solution of methyl 2-(1-(phenylsulfonyl)-1H-indol-3-yl)benzoate (150 mg, 0.38 mmol) in MeOH (5 mL) was added lithium hydroxide monohydrate (80 mg, 1.92 mmol). The mixture was heated at reflux for 18 h and cooled to room temperature before being concentrated *in vacuo.* Water (20 mL) and EtOAc (20 mL) were added and the layers separated. The aqueous portion was adjusted to pH 2 by addition of 2 M aq. HCl and then extracted with EtOAc (2 × 20 mL). The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to afford the crude carboxylic acid intermediate as a pale brown solid that was used in the subsequent step without purification. To a stirring solution of the crude carboxylic acid in CH_2Cl_2 (5 mL) was added EDCI (97 mg, 0.63 mmol), DMAP (2.31 mg, 0.019 mmol) and *N*-benzylcyclopropanamine **170a** (58.6 mg, 0.40 mmol).The resulting solution was stirred at room temperature for 18 hours. 1 M aqueous HCl (10 mL) was added and the solution was

extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound **234** (50.1 mg, 34%, 3:1 mixture of rotamers *A*:*B*) as a colourless oil; ν_{max} / cm^{-1}: 3288 (br. s), 3058 (m), 2921 (m), 1621 (s), 1612 (s), 1441 (s), 1410 (s), 1301 (s), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (1H, br. s, N<u>H</u>, *B*), 8.10 (1H, br. s, N<u>H</u>, *A*), 7.76 – 7.57 (4H, m, 2 × Ar-C<u>H</u>, *A*+*B*), 7.49 – 6.87 (24H, m, 12 × Ar-C<u>H</u>, *A*+*B*), 4.96 (1H, d, *J* = 14.5 Hz, 1 × C**2**-<u>H</u>$_2$, *A*), 4.23 – 4.13 (2H, m, 1 × C**2**-<u>H</u>$_2$, *A* and 1 × C**2**-<u>H</u>$_2$, *B*), 3.55 (1H, d, *J* = 14.5 Hz, 1 × C**2**-<u>H</u>$_2$, *B*), 2.40 (1H, tt, *J* = 7.5, 4.0 Hz, C**3**-<u>H</u>, *B*), 1.77 – 1.65 (1H, m, C**3**-<u>H</u>, *A*), 0.57 – 0.07 (8H, m, C**4**-<u>H</u>$_2$ and C**5**-<u>H</u>$_2$, *A*+*B*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7 (C**1**, *A*+*B*), 137.4, 137.3, 136.9, 136.1, 130.1, 129.8, 129.6, 129.3, 128.8, 128.7, 128.5, 127.7, 127.6, 127.3, 127.1, 126.9, 122.6, 122.4, 120.6, 120.2, 120.1, 111.8, 111.5, 102.3, 102.1, 102.1, 53.5 (C**2**, *A*), 50.5 (C**2**, *A*), 32.1 (C**3**, *B*), 28.7 (C**3**, *B*), 9.2, 8.3 (C**4** and C**5**, *A*), 7.7, 7.5 (C**4** and C**5**, *B*). *Due to the presence of rotamers and line broadening, it was not possible to confidently assign aromatic signals.* HRMS: (ESI)$^+$ Calculated for $C_{25}H_{23}N2O$: 367.1805. Found [M + H]$^+$: 367.1809.

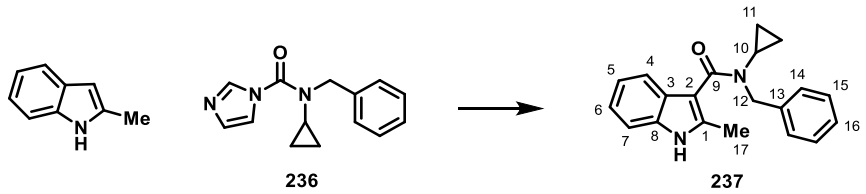
***N*-Benzyl-*N*-cyclopropyl-1*H*-imidazole-1-carboxamide (236)**



170a **236**

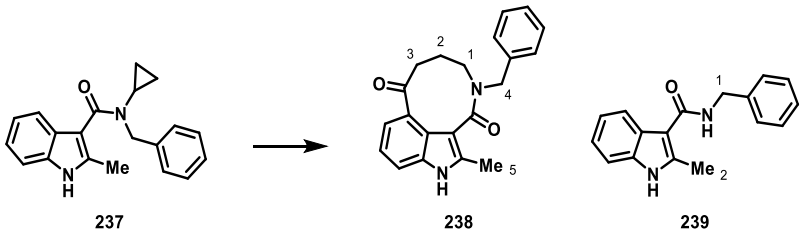
To a solution of 1,1′-carbonyldiimidazole (851 mg, 5.25 mmol) in THF (12 mL) was added *N*-benzylcyclopropanamine **170a** (515 mg, 3.50 mmol). The reaction mixture was heated at reflux for 16 hours and then cooled to room temperature. THF was removed *in vacuo* and the resulting yellow residue was dissolved in CH_2Cl_2 (30 mL), washed with H_2O (2 × 20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified through a short pad of silica eluting with EtOAc to give the title compound **236** (810 mg, 96%) as a colourless oil; ν_{max} / cm^{-1}: 3119 (m), 2952 (m), 1689 (s), 1413 (s), 1289 (s), 1254 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, d, *J* = 1.0 Hz, C**1**-<u>H</u>), 7.43 – 7.28 (6H, m, C**3**-<u>H</u>, 2 × C**7**-<u>H</u>, 2 × C**8**-<u>H</u> and C**9**-<u>H</u>), 7.07 (1H, m, C**2**-<u>H</u>), 4.71 (2H, s, C**5**-<u>H</u>$_2$), 2.68 (1H, tt, *J* = 7.0, 4.0 Hz, C**10**-<u>H</u>), 0.85 – 0.76 (2H, m, C**11**-<u>H</u>$_2$), 0.66 – 0.60 (2H, m, C**11**-<u>H</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.1 (C**4**), 137.3 (C**1**), 136.5 (C**6**), 129.4 (C**2**), 129.0, 128.3 128.1 (C**7**, C**8** and C**9**), 118.3 (C**3**), 53.3 (C**5**), 31.8 (C**10**), 10.1 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{14}H_{16}N_3O$: 242.1288. Found [M + H]$^+$: 242.1292.

***N*-Benzyl-*N*-cyclopropyl-2-methyl-1*H*-indole-3-carboxamide (237)**



The title compound was prepared following a modified literature procedure.[172] To a solution of 2-methylindole (218 mg, 1.60 mmol) and imidazole **236** (350 mg, 1.60 mmol) in toluene (10 mL) at 0 °C was added $AlMe_3$ (2.4 mL, 1.80 mmol, 2.0 M in toluene) dropwise over 10 minutes. After addition was complete, stirring was maintained for a further 45 minutes, after which time the reaction was heated at 105 ℃ for 4 hours. The mixture was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ (8 mL). The solution was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (50% EtOAc/toluene) to afford the title compound (340 mg, 70%) as an off-white solid; m.p.: 161–162 °C (MeOH); ν_{max} / cm^{-1}: 3133 (br. s), 2982 (m), 1625 (s), 1444 (s), 1313 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (1H, br. s, N<u>H</u>), 7.39 (1H, m, C**4**-<u>H</u>), 7.34 – 7.25 (5H, m, 2 × C**14**-<u>H</u>, 2 × C**15**-<u>H</u> and C**16**-<u>H</u>), 7.14 – 6.94 (3H, m, C**5**-<u>H</u>, C**6**-<u>H</u> and C**7**-<u>H</u>), 4.71 (2H, s, C**12**-<u>H_2</u>), 2.58 (1H, m, C**10**-<u>H</u>), 2.20 (3H, s, C**17**-<u>H_3</u>), 0.60 (4H, s, 2 × C**11**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9 (C**9**), 138.2 (Ar-C), 135.0 (2 signals, 2 × Ar-C), 128.7, 128.0, 127.4 (C**14**, C**15** and C**16)**, 126.3 (C**3**), 121.5, 120.4 (C**5** and C**6**), 118.8 (C**4**), 111.1 (C**7**), 52.7 (C**12**), 39.1 (C**10**), 12.4 (C**17**), 8.7 (C**11**); HRMS: $(ESI)^+$ Calculated for $C_{20}H_{21}N_2O$: 305.1648. Found $[M + H]^+$: 305.1639.

10-Benzyl-1-methyl-7,8,9,10-tetrahydro-2*H*-azonino[3,4,5-*cd*]indole-6,11-dione (238) and ***N*-benzyl-2-methyl-1*H*-indole-3-carboxamide (239)**



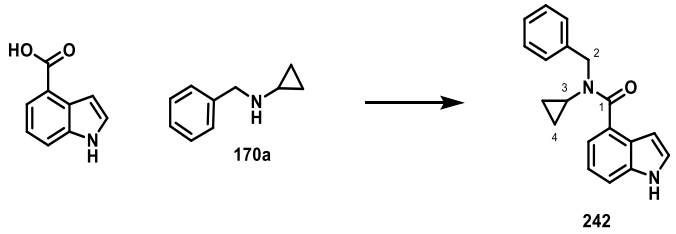
<u>General Procedure C:</u> *In a modification to General procedure C, 1-adamantanecarboxylic acid (50 mol%) was used instead of 2-$NO_2C_6H_4COOH$ (150 mol%).* Indole **237** (30.4 mg, 0.10 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. *An in situ yield could not be obtained by ^{1}H NMR spectroscopy due to broad and overlapping signals at room temperature.* The residue was purified by flash column chromatography (50% EtOAc/toluene); however, the product **238** could not be readily separated from the ligand, starting material and other side products. The structure of product **238** was determined by analysis of the ^{1}H NMR spectrum of partially purified material and corroborated

by COSY data and HRMS. Analysis of the ^{1}H NMR spectrum of the mixture indicated formation of product **238** due to the presence of characteristic peaks. A ^{1}H NMR spectrum was recorded at 100 °C in DMSO-d_6 because at room temperature slow conformational interconversion of **238** gave a broad spectrum. The signals for C**1**-$\underline{H}_2$, C**2**-$\underline{H}_2$ and C**3**-$\underline{H}_2$, coalesced at 100 °C but they were not resolved.

Data for **238**: *Characteristic signals only:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (2H, br. m, C**1**-$\underline{H}_2$), 2.84 (2H, br. m, C**3**-$\underline{H}_2$); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 3.41 (2H, br. m, C**1**-$\underline{H}_2$), 2.63 (2H, br. m, C**3**-$\underline{H}_2$), 1.85 (2H, br. m, C**2**-$\underline{H}_2$); HRMS: (ESI)$^+$ Calculated for $C_{22}H_8N_2NaO_2$: 355.0478. Found [M + Na] $^+$: 355.0478.

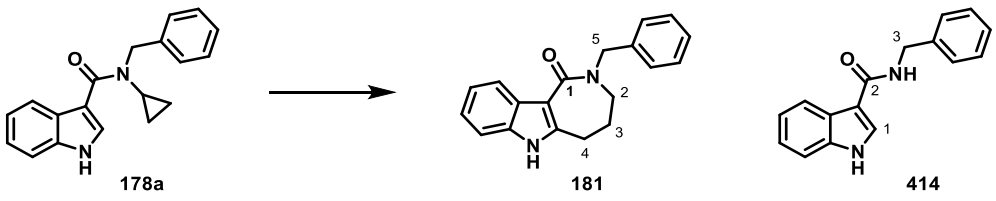
Data for **239**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.68 (1H, d, J = 5.5 Hz, C**1**-$\underline{H}_2$); HRMS: (ESI)$^+$ Calculated for $C_{17}H_{16}N_2O$: 265.0914. Found [M + H] $^+$: 265.0913.

***N*-Benzyl-*N*-cyclopropyl-1H-indole-4-carboxamide (242)**



General Procedure B: 1H-indole-4-carboxylic acid 1*H*-Pyrrole-2-carboxylic acid (322 mg, 2.00 mmol) and *N*-benzylcyclopropylamine **170a** (309 g, 2.10 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue was purified by flash column chromatography (10% EtOAc/CH_2Cl_2) to give the title compound **242** (335 mg, 58%) as a colourless solid; m.p.: 171–173 °C (MeOH); ν_{max} / cm^{-1}: 3257 (br. s), 2918 (m), 1616 (s), 1589 (s), 1429 (s), 1295 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (1H, br. s, N$\underline{H}$), 7.57 – 7.28 (6H, m, 6 × ArC-$\underline{H}$), 7.24 – 7.14 (3H, m, 3 × ArC-$\underline{H}$), 6.47 (1H, d, *J* = 2.5 Hz, ArC-$\underline{H}$), 4.78 (2H, s, C**2**-$\underline{H}_2$), 2.58 (1H, tt, *J* = 7.0, 4.0 Hz, C**3**-$\underline{H}$), 0.50 (4H, br. m, 2 × C**4**-$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3 (C**1**), 138.1 (Ar$\underline{C}$), 136.1 (Ar$\underline{C}$), 129.2 (Ar$\underline{C}$), 128.6 (Ar-$\underline{C}$H), 128.2 (Ar-$\underline{C}$H), 127.3 (Ar-$\underline{C}$H), 125.4 (2 signals, Ar$\underline{C}$ and Ar-$\underline{C}$H), 121.2 (Ar-$\underline{C}$H), 118.6 (Ar-$\underline{C}$H), 112.4 (Ar-$\underline{C}$H), 101.4 (Ar-$\underline{C}$H), 51.0 (C**2**), 31.3 (C**3**), 8.9 (C**4**); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{18}N_2NaO$: 313.1311. Found [M + Na] $^+$: 313.1322.

2-Benzyl-2,3,4,5-tetrahydro-1*H*-azocino[4,3-b]indole-1,6(7*H*)-dione (181) and ***N*-Benzyl-1*H*-indole-3-carboxamide (414)**



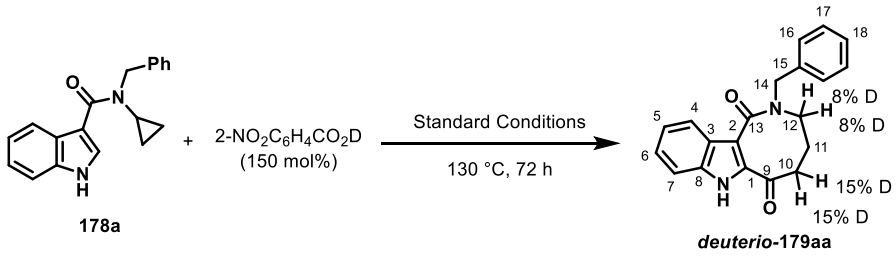
General Procedure C: *In a modification to General procedure C, the reagents were dissolved in argon sparged anhydrous 1,2-DCB (0.10 M).* Indole **178a** (29.0 mg, 0.10 mmol) was employed and the reaction mixture was heated at 130 °C for 48h. *An in situ yield was obtained by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard; a 5% yield of cyclised product **181** was observed.* Flash column chromatography (20% EtOAc/toluene) afforded the desired product **181** and an NH by-product **414** as colourless oils. *Due to small quantity of product **181** this compound was not isolated as a pure compound. The structure of **181** was determined by analysis of the ^{1}H NMR, COSY, HMBC spectra and mass spectrometry.*

Data for **181**: *Characteristic peaks only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (2H, s, C**5**-$\underline{H}_2$), 3.26 (2H, t, *J* = 7.0 Hz, C**2**-$\underline{H}_2$), 2.45 (2H, t, *J* = 8.0 Hz, C**4**-$\underline{H}_2$), 2.03 – 1.95 (2H, m, C**3**-$\underline{H}_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.8 (C**1**), 46.6, 46.5 (C**2**, C**5**), 31.0 (C**4**) 17.7 (C**3**); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{19}N_2O$: 291.1491. Found [M + H] $^+$: 291.1492.

Data for **414**: *Characteristic peaks only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (1H, d, *J* = 3.0 Hz, C**1**-$\underline{H}$), 6.24 (1H, br. s, N$\underline{H}$), 4.72 (2H, d, *J* = 5.5 Hz, C**3**-$\underline{H}_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.1 (C**1**), 43.6 (C**3**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{15}N_2O$: 251.1179. Found [M + H] $^+$: 251.1181. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[346]

7.3.2 Mechanistic studies from Chapter 2

Eqn 1: Deuterium exchange experiment of the carbonylative cyclisation of indole 178a with 2-$NO_2C_6H_4CO_2D$

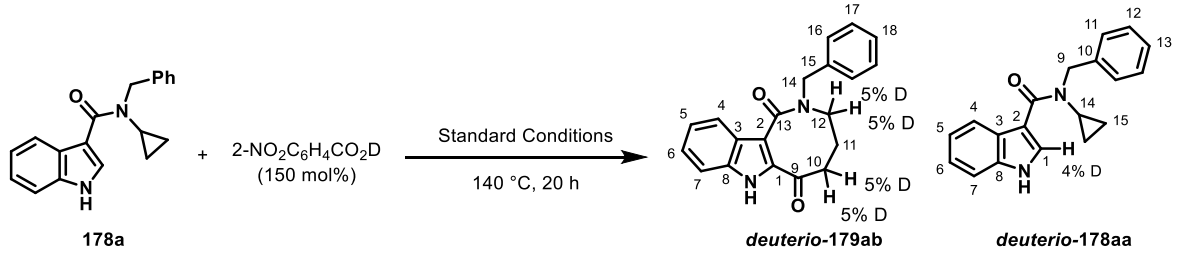


2-$NO_2C_6H_4CO_2D$ was prepared by repeatedly dissolving 2-$NO_2C_6H_4CO_2H$ in MeOD-d_4 and concentrating the resulting solution *in vacuo*.

General Procedure C: Indole **178a** (43.5 mg, 0.15 mmol) and *o*-$NO_2C_6H_4CO_2D$ (37.8 mg, 0.15 mmol) were employed and the reaction mixture was heated at 130 °C for 72 h. The residue was purified by flash column chromatography (5–10% acetone/toluene) to afford ***deuterio*-179aa** (18.3 mg, 38%). The percentage of deuterium incorporation was measured by ^{1}H NMR analysis. Analysis of ***deuterio*-179aa** revealed 8% and 8% deuterium incorporation at the diastereotopic C**12** protons, and 15% and 15% deuterium incorporation at the diastereotopic C**10** protons. <5% deuterium incorporation was measured at N$\underline{H}$. The sites of deuterium incorporation were also unambiguously confirmed by ^{2}H NMR analysis.

Data for product ***deuterio*-179aa**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.28 (1H, br. s, N<u>H</u>), 8.12 (1H, d, *J* = 8.5, C**4**-<u>H</u>), 7.44 – 7.26 (8H, m, C**5**-<u>H</u>, C**6**-<u>H</u>, C**7**-<u>H</u>, 2 × C**16**-<u>H</u>, 2 × C**17**-<u>H</u> and C**18**-<u>H</u>), 5.32 (1H, d, *J* = 14.5 Hz, 1 × C**14**-<u>H</u>$_2$), 4.53 (1H, d, *J* = 14.5 Hz, 1 × C**14**-<u>H</u>$_2$), 3.82 (0.92H, m, 1 × C**12**-<u>H</u>$_2$), 3.30 (0.92H, m, 1 × C**12**-<u>H</u>$_2$), 3.12 (0.85H, m, 1 × C**10**-<u>H</u>$_2$), 2.63 (0.85H, m, 1 × C**10**-<u>H</u>$_2$), 2.08 (1H, m, 1 × C**11**-<u>H</u>$_2$), 1.84 (1H, m, 1 × C**11**-<u>H</u>$_2$); ^{2}H NMR (77 MHz): δ 2.97 (0.15D, br. m), 2.48 (0.15D, br. m,), 1.80 (0.16D, br. m).

Eqn 2: Deuterium exchange experiment of the carbonylative cyclisation of indole 178a with 2-$NO_2C_6H_4CO_2D$



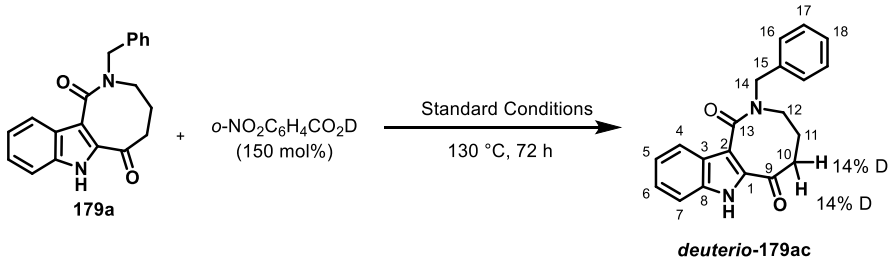
178a ***deuterio*-179ab** ***deuterio*-178aa**

<u>General Procedure C:</u> Indole **178a** (31.8 mg, 0.10 mmol) and 2-$NO_2C_6H_4CO_2D$ (25.2 mg, 0.15 mmol) were employed and the reaction mixture was heated at 140 °C for 20 h. The residue was purified by flash column chromatography (5–20% acetone/toluene) to afford ***deuterio*-179ab** (6.20 mg, 13%) and ***deuterio*-178aa** (35.0 mg, 81%). The percentage of deuterium incorporation was measured by ^{1}H NMR. Analysis of ***deuterio*-179ab** revealed 5% and 5% deuterium incorporation at the diastereotopic C**12** protons and 5% and 5% deuterium incorporation at the diastereotopic C**10** protons**.** The deuterium incorporation was also unambiguously confirmed by ^{2}H NMR. Analysis of ***deuterio*-178aa** revealed 4% deuterium incorporation at C**1** proton and 14% at N<u>H</u> protons. The deuterium incorporation was also unambiguously confirmed by ^{2}H NMR.

Data for product ***deuterio*-179ab**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (1H, br. s, N<u>H</u>), 8.12 (1H, d, *J* = 8.5, C**4**-<u>H</u>), 7.46 – 7.24 (8H, m, C**5**-<u>H</u>, C**6**-<u>H</u>, C**7**-<u>H</u>, 2 × C**16**-<u>H</u>, 2 × C**17**-<u>H</u> and C**18**-<u>H</u>), 5.31 (1H, d, *J* = 14.5 Hz, 1 × C**14**-<u>H</u>$_2$), 4.53 (1H, d, *J* = 14.5 Hz, 1 × C**14**-<u>H</u>$_2$), 3.82 (0.95H, m, 1 × C**12**-<u>H</u>$_2$), 3.31 (0.95H, m, 1 × C**12**-<u>H</u>$_2$), 3.12 (0.95H, m, 1 × C**10**-<u>H</u>$_2$), 2.63 (0.95H, m, 1 × C**10**-<u>H</u>$_2$), 2.08 (1H, m, 1 × C**11**-<u>H</u>$_2$), 1.84 (1H, m, 1 × C**11**-<u>H</u>$_2$); ^{2}H NMR (77 MHz): δ 3.21 (0.10D, br. m), 2.60 (0.05D, br. m,), 2.01 (0.05D, br. m).

Data for recovered starting material ***deuterio*-178aa**: ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.73 (0.86H, s, N<u>H</u>), 8.02 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-<u>H</u>), 7.80 (0.96D, d, *J* = 3.0 Hz, C**1**-<u>H</u>), 7.46 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-<u>H</u>), 7.37 – 7.30 (4H, m 2 × C**11**-<u>H</u> and 2 × C**12**-<u>H</u>), 7.26 (1H, m, C**13**-<u>H</u>), 7.20 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**6**-<u>H</u>), 7.14 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-<u>H</u>), 4.79 (2H, s, C**9**-<u>H</u>$_2$), 2.86 (1H, tt, *J* = 7.0, 4.0 Hz, C**14**-<u>H</u>), 0.75 – 0.61 (4H, m, 2 × C**15**-<u>H</u>$_2$); ^{2}H NMR (77 MHz,) δ 9.71 (0.02D, s), 7.83 (0.04D, s, C**1**-<u>H</u>).

Eqn 3: Deuterium exchange experiment of indole 179a with 2-$NO_2C_6H_4CO_2D$ under standard reaction conditions

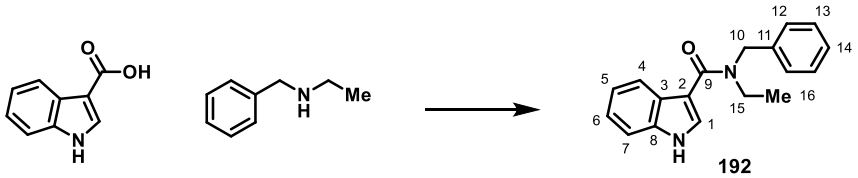


General Procedure C: Indole **179a** (31.8 mg, 0.10 mmol) and 2-$NO_2C_6H_4CO_2D$ (25.2 mg, 0.15 mmol) were employed and the reaction mixture was heated at 130 °C for 72 h. The residue was purified by flash column chromatography (10–20% acetone/toluene) to afford ***deuterio*-179ac** (25.6 mg, 81%). The percentage of deuterium incorporation was measured by ^{1}H NMR. Analysis of ***deuterio*-179ac** revealed 14% and 14% deuterium incorporation at the diastereotopic C**10** protons. <5% deuterium incorporation was measured at NH proton. The deuterium incorporation was also unambiguously confirmed by ^{2}H NMR analysis.

Data for product ***deuterio*-179ac**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (1H, br. s, NH), 8.12 (1H, dd, *J* = 8.5, 1.0 Hz, C**4**-H), 7.44 – 7.26 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 5.32 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 4.53 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H_2), 3.82 (1H, m, 1 × C**12**-H_2), 3.37 (1H, m, 1 × C**12**-H_2), 3.13 (0.86H, m, 1 × C**10**-H_2), 2.63 (0.86H, m, 1 × C**10**-H_2), 2.08 (1H, m, 1 × C**11**-H_2), 1.85 (1H, m, 1 × C**11**-H_2); H NMR ($CHCl_3$, 77 MHz): δ 2.95 – 2.48 (0.28D, br. m, C**10**-H_2).

*These results support the hypothesis that deuterium incorporation at C**10** occurs via enolization of the product.*

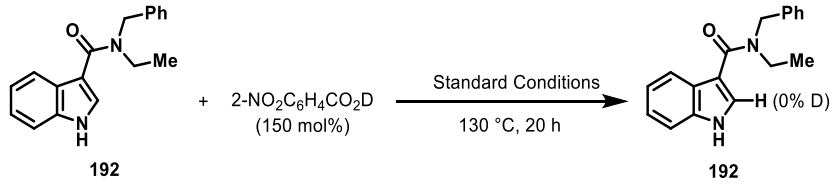
***N*-Benzyl-*N*-ethyl-1*H*-indole-3-carboxamide (192)**



General Procedure B: 1*H*-Indole-3-carboxylic acid (500 mg, 3.11 mmol) and *N*-benzylethanamine (417 mg, 3.11 mmol) were employed and the reaction was stirred at room temperature for 18 hours. The crude residue recrystallised from MeOH to give the title compound **192** (412g, 48%) as a colourless solid; m.p.: 155–157 °C (MeOH); ν_{max}/ cm^{-1}: 3206 (br. s), 2961 (s), 1591 (s), 1568 (s), 1432 (s), 1200 (s); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.49 (1H, s, NH), 7.78 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.57 (1H, m, C**1**-H), 7.43 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.39 – 7.25 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.19 –

7.07 (2H, m, C**5**-H and C**6**-H), 4.75 (2H, s, C**10**-H_2), 3.44 (2H, q, *J* = 7.0 Hz, C**15**-H_2), 1.13 (3H, t, *J* = 7.0 Hz, C**16**-H_3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.3 (C**9**), 138.5 (C**11**), 135.6 (C**8**), 128.6 (C**13**), 127.1, 127.0, 126.6, 126.2 (C**1**, C**3**, C**12** and C**14**), 121.9 (C**6**), 120.4, 120.1 (C**4** and C**5**), 111.8 (C**7**), 109.9 (C**2**), 49.0 (C**10**), 41.4 (C**15**), 13.4 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{18}H_{18}N_2NaO$: 301.1311. Found [M + Na]$^+$: 301.1325.

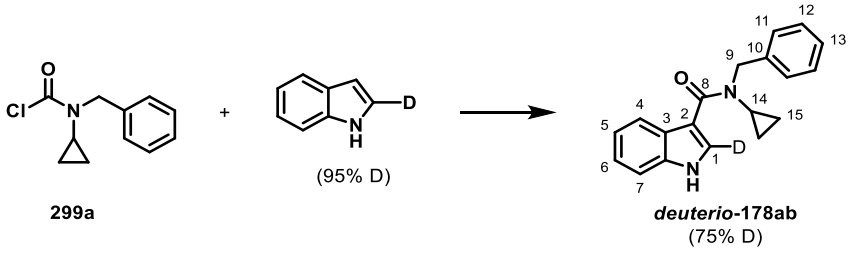
Eqn 4: Deuterium exchange experiment of indole 192 with 2-$NO_2C_6H_4CO_2D$ under standard reaction conditions



General Procedure C: Indole **192** (41.7 mg, 0.15 mmol) and 2-$NO_2C_6H_4CO_2D$ (37.8 mg, 0.15 mmol) were employed and the reaction mixture was heated at 130 °C for 20 h. The residue was purified by flash column chromatography (10–20% acetone/toluene) to afford recovered **192** (27.9 mg, 67%). The percentage of deuterium incorporation was measured by ^{1}H NMR analysis, which revealed no deuterium incorporation.

Intramolecular kinetic isotope effect experiment

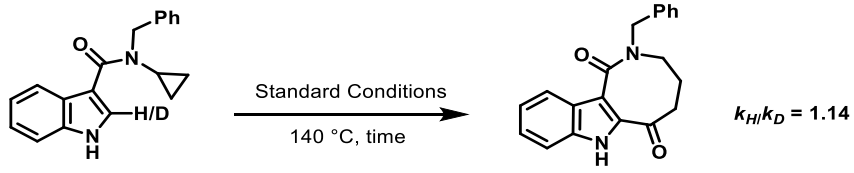
***N*-Benzyl-*N*-cyclopropyl-1*H*-indole-3-carboxamide-2-*d* (*deuterio*-178ab)**



To a suspension of 1*H*-indole-2-*d* (354 mg, 3.00 mmol) (prepared according to the literature procedure[347]) and $AlCl_3$ (480 mg, 3.60 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C was added a solution of benzyl(cyclopropyl)carbamic chloride **299a** (1.03 g, 3.60 mmol) in CH_2Cl_2 (10.0 mL). The resulting solution was stirred at 0 °C for 4 hours and then allowed the warm to room temperature. The reaction mixture was quenched by addition of H_2O (35 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10–20% EtOAc/CH_2Cl_2) to afford ***deuterio*-178ab** (264 mg, 30%) as an off-white solid. The percentage of deuterium incorporation was measured by ^{1}H NMR analysis, which revealed 75% deuterium incorporation at the C**1** proton. ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ 9.65 (1H, s, NH), 7.99 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.80 (0.25H, m,

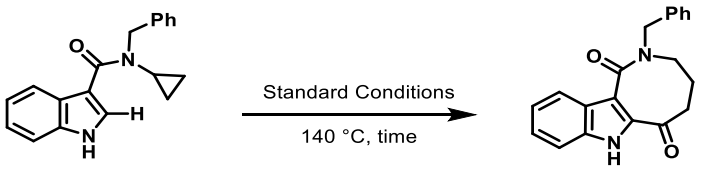
C**1**-H), 7.45 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.34 – 7.30 (4H, m, 2 × C**11**-H and 2 × C**12**-H), 7.24 (1H, m, C**13**-H), 7.19 – 7.09 (2H, m, C**5**-H and C**6**-H), 4.76 (2H, s, C**9**-H_2), 2.84 (1H, s, C**14**-H), 0.73 – 0.58 (4H, m, 2 × C**15**-H_2); ^{2}H NMR (77 MHz,) δ 7.83 (0.75D, s, C**1**-H); HRMS: $(ESI)^+$ Calculated for $C_{19}H_{17}DN_2O$: 292.1555. Found $[M + H]^+$: 292.1549.

Eqn 5: Kinetic isotope effect determination for the Rh(I)-catalysed carbonylative cyclisation of 178 and *deuterio*-178ab.



178a/*deuterio*-178ab **179a/*deuterio*-179ad**

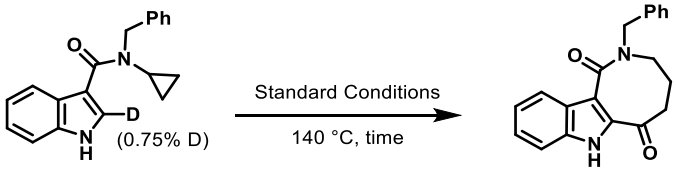
Five identical, oven dried reaction tubes were fitted with a magnetic stirrer and charged with **178a** (29.0 mg, 100 mol%), $[Rh(cod)OMe]_2$ (1.84 mg, 3.75 mol%), P-(4-(F)$C_6H_4)_3$ (7.11 mg, 22.5 mol%) and 2-$NO_2C_6H_4CO_2H$ (25.5 mg, 150 mol%). Each tube was fitted with a rubber septum and purged with argon for 20 minutes. The reagents were dissolved in argon sparged anhydrous PhCN (0.30 M). The reaction vessel was purged with CO for approximately 10 minutes and the suspension was subsequently sparged with CO for approximately 30 seconds. Each reaction tube was heated at 140 °C under a CO atmosphere (1 atm) for the time noted. The reactions were stopped at 7 h, 9 h, 11 h, 13 h and 15 h respectively. The conversion to product **179a** was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. Five analogous reaction tubes were set up using ***deuterio*-178ab** (29.1 mg, 100 mol%) and were stopped after 7 h, 9 h, 11 h, 13 h and 15 h respectively. The conversion to product ***deuterio*-179ad** was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.



178a **179a**

Entry	time (hours)	Yield **178a**[a]
1	7	6%
2	9	10%
3	11	20%
4	13	23%
5	15	32%

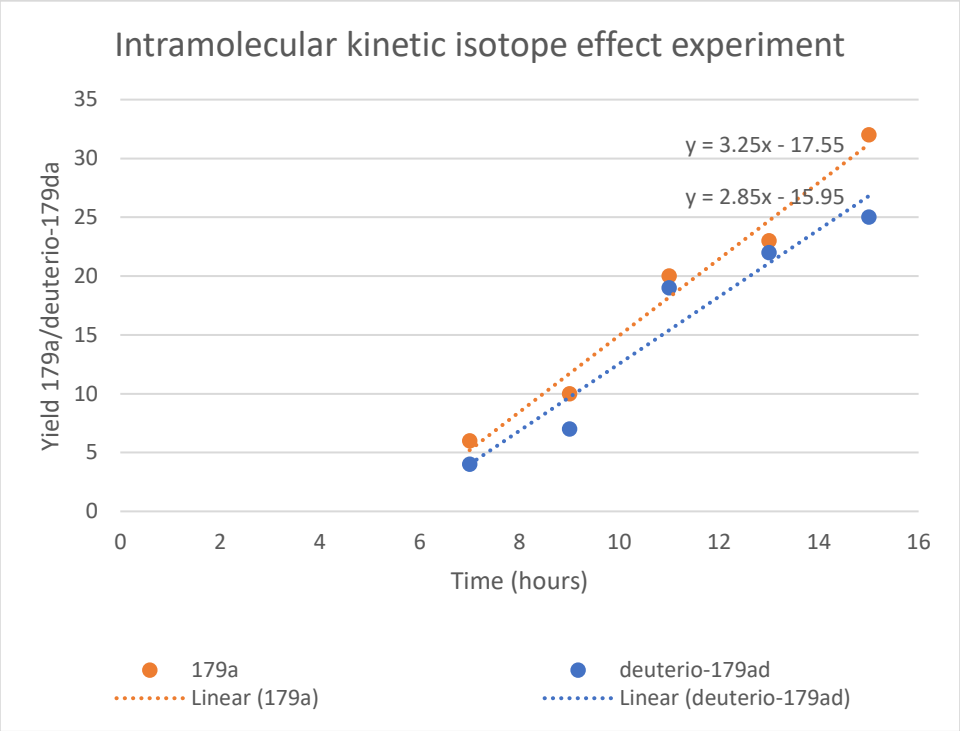
[a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.



***deuterio*178ab** ***deuterio*-179ad**

Entry	time (hours)	Yield ***deuterio*-179ad**[a]
1	7	4%
2	9	7%
3	11	19%
4	13	22%
5	15	25%

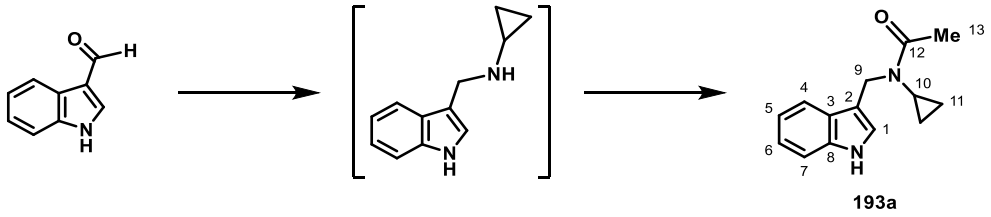
[a] The yield was determined by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard.



k_H/k_D = 3.25/2.85=1.14

Figure 5: Formation of product 179a and *deuterio*-179ad as a function of time

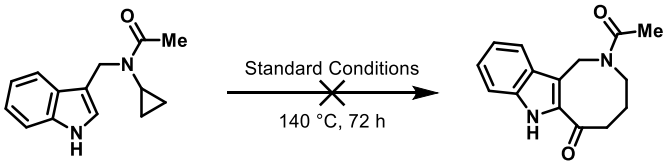
***N*-((1*H*-indol-3-yl)methyl)-*N*-cyclopropylacetamide (193a)**



A solution of 1*H*-indole-3-carbaldehyde (290 mg, 2.00 mmol) and cyclopropylamine (0.15 mL, 2.20 mmol) in MeOH (10.0 mL) was heated at reflux for 2 hours. The resulting suspension was cooled to 0 °C and $NaBH_4$ (91.0 mg, 2.40 mmol) was added portion wise over 10 minutes. The reaction was warmed to room temperature and stirred for an additional 16 hours. The reaction mixture was concentrated *in vacuo* before the addition of saturated aqueous $NaHCO_3$ (20 mL). The solution was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude amine intermediate which was used without further purification. The crude material was re dissolved in CH_2Cl_2 (10.0 mL) and the solution was cooled to 0 °C. Et_3N (0.42 mL, 3.00 mmol) was added, followed by dropwise addition of acetyl chloride (0.14 mL, 2.00 mmol) over 5 minutes. The reaction mixture was warmed to room temperature and stirred for a further 3 hours. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude

residue was purified by flash column chromatography (60–70% EtOAc/hexane) to give the title compound **193a** (395 mg, 87%) as an off-white solid; m.p.: 155–157 °C (MeOH); ν_{max}/ cm^{-1}: 3288 (br. s), 2058 (m), 1621 (s), 1442 (s), 1410 (s), 1310 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (1H, br. s, NH), 7.74 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.36 (dd, *J* = 8.0, 1.0 Hz, C**7**-H), 7.22 – 7.17 (2H, m, C**1**-H and C**6**-H), 7.13 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-H), 4.75 (2H, s, C**9**-H_2), 2.47 (1H, tt, *J* = 6.5, 4.0 Hz, C**10**-H), 2.21 (3H, s, C**13**-H_2), 0.88 – 0.80 (4H, m, 2 × C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6 (C**12**), 136.2 (C**8**), 127.1 (C**3**), 124.3 (C**1**), 122.1 (C**6**), 119.7 (C**5**), 119.4 (C**4**), 113.0 (C**2**), 111.3 (C**7**), 40.7 (C**9**), 30.3 (C**10**), 22.9 (C**13**), 9.6 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{14}H_{16}N_2NaO$: 251.1155. Found [M + Na]$^+$: 251.1147.

Attempted Rh(I)-catalysed carbonylation of indole 193a



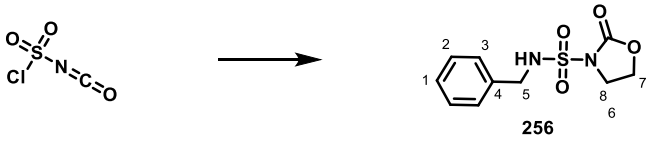
193a **194a**

General Procedure C: Compound **193a** (34.2 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 48 h. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed decomposition and none of the desired product **194a**.

7.4 Experimental procedures for the studies in Chapter 3

7.4.1 Synthesis of substrates and catalysis products

***N*-Benzyl-2-oxooxazolidine-3-sulfonamide (256)**

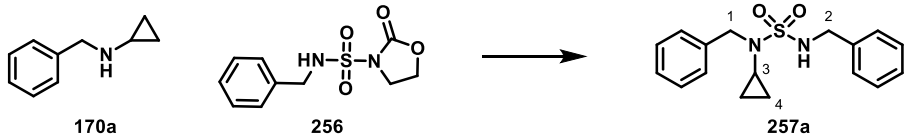


256

*The title compound **255** was prepared following a literature procedure*.[182] Chlorosulfonylisocyanate (2.18 mL, 25.0 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. 2-Chloroethanol (1.67 mL, 25.0 mmol) was dissolved in dry CH_2Cl_2 (8 mL) and added dropwise over 30 minutes. A mixture of benzylamine (3.00 mL, 27.5 mmol) and triethylamine (7.67 mL, 55.0 mmol) in CH_2Cl_2 (15 mL) was added over 10 minutes. The mixture was warmed to room temperature and stirred for 1 hour. 0.2 M aqueous HCl (25 mL) was added and the pH was adjusted to 2 by the addition of conc. HCl. The organic layer was washed with 0.05 M aqueous HCl (25 mL), H_2O (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound **256** (4.16 g, 65%) as an off-white solid; ^{1}H NMR (400

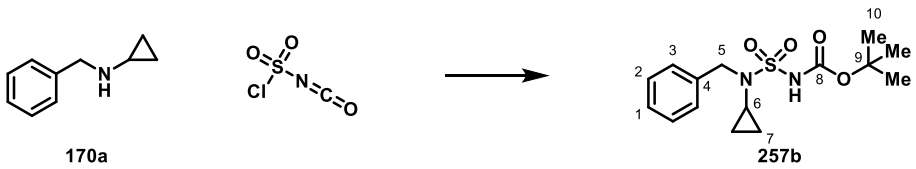
MHz, CD_3CN): δ 7.46 – 7.27 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 6.35 (1H, t, *J* = 6.0 Hz, NH), 4.31 (2H, t, *J* = 7.0, C**7**-H_2), 4.25 (2H, d, *J* = 6.0 Hz, C**5**-H_2), 3.74 (2H, t, *J* = 7.0, C**8**-H_2); ^{13}C NMR (101 MHz, CD_3CN): δ 153.0 (C**6**), 137.8 (C**4**), 129.5, 129.1 (C**2**, C**3**), 128.7 (C**1**), 66.6 (C**7**), 48.4 (C**8**), 43.1 (C**5**). *The spectroscopic properties of this compound were consistent with the data available in the literature*.[348]

***N*,*N*'-Dibenzyl-*N*-cyclopropylsulfamide (257a)**



To a solution of *N*-benzylcyclopropanamine **170a** (3.01 g, 22.5 mmol) and triethylamine (5.64 mL, 40.5 mmol) in MeCN (60 mL) was added *N*-benzyl-2-oxooxazolidine-3-sulfonamide **256** (3.50 g, 14.0 mmol). The reaction mixture was heated to reflux for 16 hours and then cooled to room temperature. The volatiles were removed *in vacuo* and the crude residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **257a** (3.72 g, 84%) as an off-white solid; m.p.: 66–67 °C (EtOAc); ν_{max}/ cm^{-1}: 3296 (br. m), 2987 (m), 1454 (s), 1328 (s), 1150 (s), 1066 (s), 1027 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (2H, m, ArC-H), 7.38 – 7.28 (6H, m, ArC-H), 7.23 (2H, dd, *J* = 7.8, 1.7 Hz, ArC-H), 4.42 (2H, s, C**1**-H_2), 4.37 (1H, t, *J* = 6.0 Hz, NH), 4.09 (2H, d, *J* = 6.0 Hz, C**2**-H_2), 2.39 (1H, tt, *J* = 6.5, 4.0 Hz, C**3**-H), 0.81 – 0.64 (4H, m, 2 × C**4**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.0 (ArC), 136.8 (ArC), 129.1, 128.9, 128.6, 128.4 (2 signals), 127.9 (6 × Ar-CH), 55.2 (C**2**), 47.6 (C**1**), 30.4 (C**3**), 7.8 (C**4**); HRMS: (ESI$^+$) Calculated for $C_{17}H_{21}N_2O_2S$: 317.1318. Found $[M + H]^+$: 317.1338.

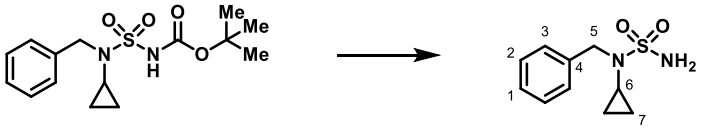
***tert*-Butyl (*N*-benzyl-*N*-cyclopropylsulfamoyl)carbamate (257b)**



To a solution of chlorosulfonylisocyanate (0.39 mL, 4.50 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *t*-BuOH (0.43 mL, 4.50 mmol). The solution was stirred at 0 °C for 10 minutes and then allowed to warm to room temperature. A solution of *N*-benzylcyclopropanamine **170a** (695 mg, 4.73 mmol) and triethylamine (1.25 mL, 9.00 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture over 10 minutes and the resulting yellow suspension was stirred for an additional 1 hour. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1 M aqueous HCl (2 × 25 mL). The organic layers were combined and washed with H_2O (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the

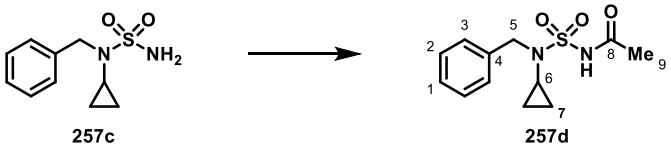
title compound **257b** (1.21 g, 83%) as an off-white solid; m.p.: 139–141 °C (EtOAc); ν_{max}/ cm^{-1}: 3300 (br. m), 3273 (m), 1715 (s), 1398 (s), 1148 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 – 7.27 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 7.07 (1H, s, NH), 4.60 (2H, s, C**5**-H_2), 2.57 (1H, m, C**6**-H), 1.49 (9H, s, 3 × C**10**-H_3), 0.85 – 0.65 (4H, m, 2 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8 (C**8**), 137.2 (C**4**), 128.7, 128.3 (C**2**, C**3**) 127.8 (C**1**), 83.7 (C**9**), 56.0 (C**5**), 31.0 (C**6**), 28.2 (C**10**), 7.3 (C**7**); HRMS: (ESI^+) Calculated for $C_{15}H_{22}N_2NaO_4S$: 349.1192. Found $[M + Na]^+$: 349.1190.

***N*-Benzyl-*N*-cyclopropylsulfamide (257c)**



To a solution of sulfamide **257b** (250 mg, 0.77 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added trifluoracetic acid (0.27 mL, 2.31 mmol). After 2 hours, the ice bath was removed and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, washed with H_2O (20 ml), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound **257c** (167 mg, 96%) as a white solid which was used without further purification; m.p.: 124–126 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 3745 (br. m), 3156 (m), 2939 (m), 1554 (s), 1398 (s), 1300 (s), 1163 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.32 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 4.43 (2H, s, C**5**-H_2), 4.15 (2H, br. s, NH_2), 2.36 (1H, tt, *J* = 7.0, 3.5 Hz, C**6**-H), 0.94 – 0.70 (4H, m, 2 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.9 (C**4**), 129.1, 128.8 (C**2,** C**3**), 128.3 (C**1**), 55.2 (C**5**) 30.2 (C**6**), 7.9 (C**7**); HRMS: (ESI^+) Calculated for $C_{10}H_{14}N_2NaO_2S$: 249.0668. Found $[M + Na]^+$: 249.0666.

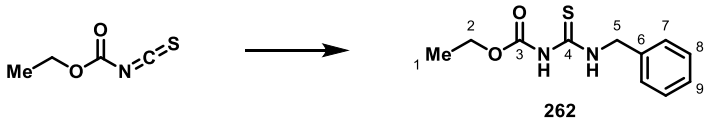
***N*-(*N*-Benzyl-*N*-cyclopropylsulfamoyl)acetamide (257d)**



To a solution of sulfamide **257c** (200 mg, 0.88 mmol) in pyridine (6 mL) was added acetyl chloride (70 µL, 0.97 mmol). The reaction mixture was stirred at room temperature for 6 hours and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous NH_4Cl (20 mL), H_2O (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound **257d** (161 mg, 68%) as a colourless solid; m.p.: 112–114 °C (EtOAc); ν_{max}/ cm^{-1}: 3130 (m), 2986 (m), 1688 (s), 1469 (s), 1427 (s), 1361 (s), 1240 (s), 1162 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (1H, s, NH),

7.44 – 7.25 (5H, m, C**1**-H, 2 × C**2**-H, 2 × C**3**-H), 4.61 (2H, s, C5-H_2), 2.59 (1H, m, C**6**-H), 2.06 (3H, s, C**9**-H_3), 0.84 – 0.66 (4H, m, 2 × C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5 (C**8**), 136.9 (C**4**), 128.6, 128.2 (C**3**, C**2**), 127.7 (C**1**), 55.6 (C**5**), 31.1 (C**6**), 23.4 (C**9**), 7.2 (C**7**); HRMS: (ESI^+) Calculated for $C_{12}H_{16}N_2NaO_3S$: 291.0774. Found $[M + Na]^+$: 291.0779.

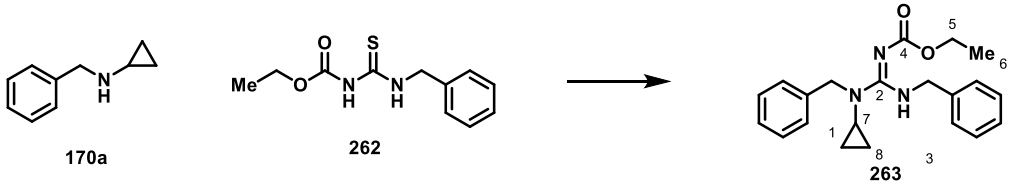
***N*-Ethoxycarbonyl-*N*'-benzyl-thiourea (262)**



262

Ethoxycarbonyl isothiocyanate (787 mg, 6.00 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. A solution of benzylamine (0.643 g, 6.00 mmol) in CH_2Cl_2 (5 mL) was added over 10 minutes and the reaction mixture was warmed to room temperature and stirred for 1 hour. The solution was diluted with CH_2Cl_2 (20 mL) and washed with 1 M aqueous HCl (25 mL). The aqueous layer was extracted twice with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, washed with H_2O (25 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound **262** (1.40 g, 98%) as an off-white solid. The product was used in the following step without any further purification. ν_{max}/ cm^{-1}: 3171 (m), 1715 (s), 1707 (s), 1549 (s), 1434 (s), 1240 (s), 1188 (s), 1046 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (1H, s, NH), 8.18 (1H, s, NH), 7.34 – 7.16 (5H, m, 2 × C**7**-H, 2 × C**8**-H, C**9**-H), 4.78 (2H, s, C**5**-H_2), 4.12 (2H, q, *J* = 7.0 Hz, C**2**-H_2), 1.21 (3H, t, *J* = 7.0 Hz, C**1**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.5 (C**4**), 152.8 (C**3**), 136.4 (C**6**), 129.0, 128.1, 128.0, (C**7,** C**8**, C**9**), 62.9 (C**2**), 49.7 (C**5**), 14.3 (C**1**); HRMS: (ESI^+): Calculated for $C_{15}H_{16}N_2NaO_2S$: 261.0668. Found $[M + Na]^+$: 261.0664. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[184]

***N*-Ethoxycarbonyl-*N*', *N*''-dibenzyl-*N*''-cyclopropylguanidine (263)**

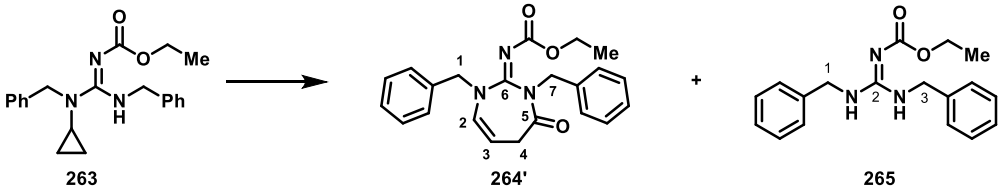


170a **262** **263**

Carbamoyl thiourea **262** (1.00 g, 4.20 mmol), *N*-benzylcyclopropanamine **170a** (0.741 g, 5.04 mmol) and triethylamine (0.59 mL, 4.20 mmol) were dissolved in CH_2Cl_2 (20 mL). EDCI (0.966 g, 5.04 mmol) was then added in one portion and the reaction mixture was stirred at room temperature for 22 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed sequentially with 1 M aqueous HCl (20 mL), water (20 mL) and brine (15 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc/toluene, modified with 1% Et_3N) to yield the title compound **263** (1.19 g, 81%) as a colourless

solid; m.p.: 110–111 °C (EtOAc); ν_{max}/ cm^{-1}: 3241 (m), 2985 (m), 1644 (s), 1558 (s), 1520 (s), 1297 (s), 1151 (s), 1095 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.13 (8H, m, 8 × ArC-H), 7.11 – 7.05 (2H, m, ArC-H), 4.56 (2H, s, C**1**-H_2), 4.44 (2H, d, *J* = 5.0 Hz, C**3**-H_2), 4.05 (2H, q, *J* = 7.0 Hz, C**5**-H_2), 2.28 (1H, tt, *J* = 6.5, 4.0 Hz, C**7**-H), 1.21 (3H, t, *J* = 7.0 Hz, C**6**-H_3), 0.79 – 0.62 (4H, m, 2 × C**8**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7 (C**2**), 161.4 (C**4**), 137.9 (ArC), 137.4 (ArC), 128.9, 128.5, 128.1, 127.9, 127.7, 127.3 (6 × Ar-CH), 60.8 (C**5**), 53.3 (C**3**), 48.2 (C**1**), 29.7 (C**7**), 14.8 (C**6**), 9.5 (C**8**); HRMS: $(ESI)^+$ Calculated for $C_{21}H_{26}N_3O_2$: 352.2020. Found $[M + H]^+$: 352.2013.

Ethyl (*Z*)-(1,3-dibenzyl-4-oxo-1,3,4,5-tetrahydro-2*H*-1,3-diazepin-2-ylidene)carbamate (264') and ***N*-Ethoxycarbonyl-*N*', *N*''-dibenzyl guanidine (265).**

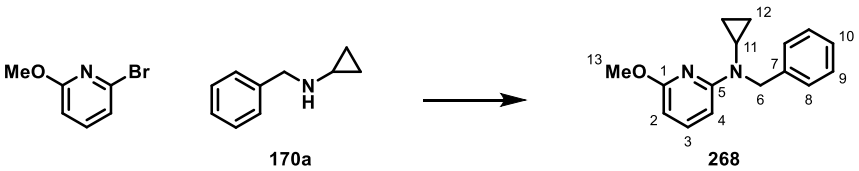


An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)OH]_2$ (2.28 mg, 5.0 μmol, 5 mol%), PPh_3 (3.24 mg, 0.015 mmol, 15 mol%), benzoic acid (3.66 mg, 0.030 mmol, 30 mol%) and guanidine substrate **263** (35.2 mg, 0.10 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged 1,2-DCB (0.5 mL). The reaction mixture was sparged with CO for approximately 10 seconds, then heated at 100 °C under a CO atmosphere for 24 h. The mixture was cooled to room temperature and concentrated *in vacuo*. *An in situ yield was obtained by ^{1}H NMR spectroscopy against 1,4-dinitrobenzene as an internal standard; a 7% yield of cyclised product **264'** was observed.* Flash column chromatography (40% EtOAc/hexane) afforded the desired product **264'** and side-product **265** as colourless oils. *Due to small quantity of product **264'** this compound was not isolated as a pure compound. The structure of **264'** was determined by analysis of the ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR spectra, mass spectrometry and by comparison to analogous products.*

Data for **264'**: *Characteristic peaks only*: ^{1}H NMR (400 MHz, $CDCl_3$): 5.97 (1H, d, *J* = 7.0 Hz, C**2**-H), 5.66 (dt, 1H, *J* = 7.0, 7.0 Hz, C**3**-H), 4.58 (2H, s, C**1**-H_2), 3.82 (2H, s, C**7**-H_2), 2.99 (2H, d, *J* = 7.0 Hz, C**4**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2 (C**5**), 153.9 (C**6**), 130.0 (C**2**), 117.4 (C**3**), 50.2, 50.0 (C**1**, C**7**), 34.8 (C**4**); HRMS: $(ESI)^+$ Calculated for $C_{22}H_{24}N_3O_3$: 378.1812. Found $[M + H]^+$: 378.1812.

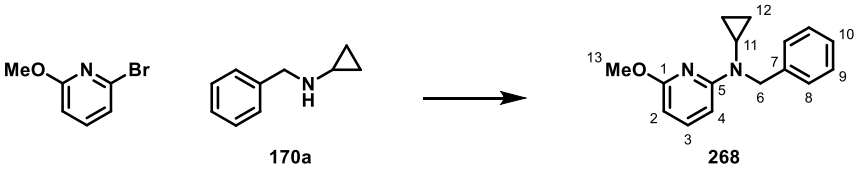
Data for **265**: *Characteristic peaks only*: ^{1}H NMR (400 MHz, $CDCl_3$): 4.80 (4H, d, *J* = 8.5 Hz, C**1**-H_2, C**7**-H_2), 4.49 (2H, br. s, 2 × NH); ^{13}C NMR (101 MHz, $CDCl_3$): 153.5 (C**2**), 54.8 (C**1**, C**3**); HRMS: $(ESI)^+$ Calculated for $C_{18}H_{22}N_3O_2$: 312.1707. Found $[M + H]^+$: 312.1718. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[184]

***N*-Benzyl-*N*-cyclopropyl-6-methoxypyridin-2-amine (268)**



To an oven dried reaction tube was added 2-bromo-6-methoxypyridine (486 mg, 2.60 mmol), *N*-benzylcyclopropanamine **170a** (458 mg, 3.12 mmol), $Pd(OAc)_2$ (29.1 mg, 0.13 mmol), dppp (107 mg, 0.26 mmol) and NaO*t*-Bu (500 mg, 5.20 mmol). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in dry toluene (13 mL). The tube was sealed and heated at 80 °C for 14 hours and then cooled to room temperature. The reaction mixture was filtered through a pad of celite® and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% toluene/hexane) to afford the title compound **268** (328 mg, 50%) as a colourless oil; υ_{max}/cm^{-1}: 2944 (m), 1589 (s), 1587 (s), 1368 (s), 1257 (s), 1149 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (1H, dd, *J* = 8.0, 8.0 Hz, C**3**-H), 7.30 – 7.17 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 6.50 (1H, dd, *J* = 8.0, 1.0 Hz, C**2**-H), 6.09 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 4.90 (2H, s, C**6**-H_2), 3.76 (3H, s, C**13**-H_3), 2.46 (1H, tt, *J* = 6.5, 3.5 Hz, C**11**-H), 0.85 – 0.79 (2H, m, 1 × C**12**-H_2), 0.74 – 0.67 (2H, m, 1 × C**12**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9 (C**1**), 158.4 (C**5**), 140.2 (C**7**), 139.7 (C**3**), 128.2, 127.4 (C**8**, C**9**) 126.5 (C**10**), 99.3 (C**2**), 97.9 (C**4**), 52.9 (C**13**), 51.8 (C**6**), 30.3 (C**11**), 8.8 (C**12**); HRMS: (ESI^+) Calculated for $C_{16}H_{19}N_2O$: 255.1419. Found $[M + H]^+$: 255.1502.

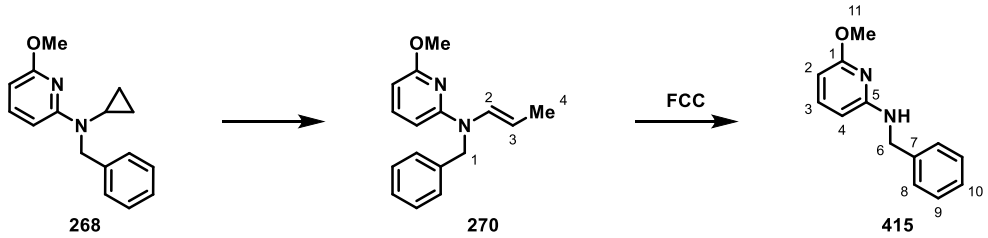
6-(Benzyl(cyclopropyl)amino)pyridin-2(1*H*)-one (269)



To a solution of pyridine **268** (600 mg, 2.37 mmol) in anhydrous MeCN (12 mL) was added NaI (710 mg, 4.74 mmol) and trimethylsilyl chloride (0.60 mL, 4.74 mmol). The solution was heated at 80 °C for 2 hours and then cooled to room temperature. MeOH (1 mL) was added and the reaction mixture was stirred for an additional 2 hours at room temperature. The volatiles were removed *in vacuo* and the residue was dissolved in EtOAc (25 mL) and washed with 10% aqueous $Na_2S_2O_3$ solution (2 × 25 mL), water (25 mL) and brine (25 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (90% EtOAc/hexane) to afford the title compound **269** (434 mg, 76%) as an off-white solid; m.p.: 98–99 °C (EtOAc); υ_{max}/cm^{-1}: 3006 (m), 2919 (m), 1654 (s), 1572 (s), 1444 (s), 1367 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.96 (1H, br. s, NH), 7.34 – 7.08 (6H, m, C**3**-H, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 5.84 (1H, d, *J* = 8.5 Hz, C**2**-H), 5.54 (1H, d, *J* = 8.0 Hz, C**4**-H), 4.67 (2H, s, C**6**-H_2), 2.62 (1H, tt, *J* = 7.0, 3.5 Hz, C**11**-H), 0.91 – 0.86

(2H, m, 1 × C**12**-H$_2$), 0.76 – 0.67 (2H, m, 1 × C**12**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3 (C**1**), 151.9 (C**5**), 142.9 (C**3**), 136. (C**7**), 128.8, 127.4, 126.3 (C**8**, C**9**, C**10**), 104.9 (C**2**), 88.9 (C**4**), 54.3 (C**6**), 30.4 (C**11**), 8.9 (C**12**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{18}N_2O$: 241.1335. Found $[M + H]^+$: 241.1337.

***N*-Benzyl-6-methoxy-*N*-(prop-1-en-1-yl)pyridin-2-amine (270) and *N*-Benzyl-6-methoxypyridin-2-amine (415)**

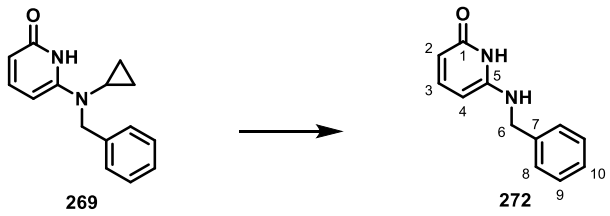


An oven dried reaction tube, fitted with a magnetic stirrer, was charged with substrate **268** (50.0 mg, 0.208 mmol), $[Rh(cod)_2]BF_4$ (4.22 mg, 10.4 µmol, 5 mol%), and PPh_3 (8.17 mg, 31.2 µmol, 15 mol%). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in anhydrous toluene (2.1 mL). The tube was sealed and the reaction mixture was heated at 140 °C for 4 hours. After this time, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. *An in situ yield was obtained by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard; a 13% yield of alkene product **270** and a 65% yield of remaining starting material **268** was observed.* The product **270** could not be isolated by column chromatography due to its instability. Flash column chromatography (FCC) (40% toluene/EtOAc) afforded the NH side-product **415** (5.2 mg, 10%) as a colourless oil. *The structure of alkene **270** was determined by analysis of the ^{1}H NMR spectrum of the reaction mixture and corroborated by COSY and HSQC data.*

Data for alkene **270**: *Characteristic peaks only:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, dd, *J* = 7.5, 1.5 Hz, C**2**-H), 5.00 (2H, s, C**1**-H$_2$), 4.87 (1H, dt, *J* = 7.5, 6.5 Hz, C**3**-H), 1.74 (3H, dd, *J* = 6.5, 1.5 Hz, C**4**-H$_3$).

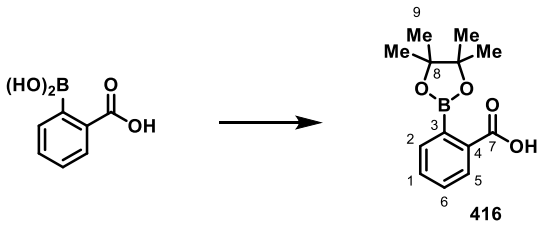
Data for amine **415**: υ_{max}/cm^{-1}: 3646 (br. m), 2901 (m), 1601 (s), 1469 (s), 1382 (s), 1242 (s), 1147 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.30 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 7.26 (1H, m, C**3**-H), 6.04 (1H, d, *J* = 8.0 Hz, C**2**-H), 5.94 (1H, d, *J* = 8.0 Hz, C**4**-H), 4.74 (1H, br. s, NH), 4.49 (2H, d, *J* = 5.5 Hz, C**6**-H$_2$), 3.84 (3H, s, C**11**-H$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.6 (C**1**), 157.5 (C**5**), 140.3 (C**3**), 139.4 (C**7**), 128.9, 127.5 (C**8**, C**9**), 127.2 (C**10**), 97.84 (C**4**), 97.6 (C**2**), 53.2 (C**11**), 46.4 (C**6**); HRMS: (ESI$^+$) Calculated for $C_{13}H_{15}N_2O$: 215.1179. Found $[M + H]^+$: 215.1185.

6-(Benzylamino)pyridin-2(1*H*)-one (272)



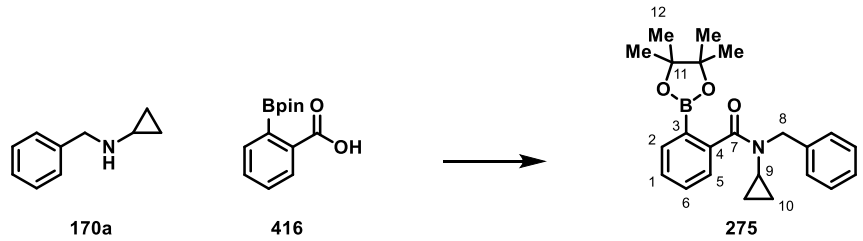
An oven dried reaction tube, fitted with a magnetic stirrer, was charged with pyridone substrate **269** (30.0 mg, 0.125 mmol), [Rh(cod)$_2$]OTf (2.93 mg, 6.25 µmol, 5 mol%), and PPh_3 (4.91 mg, 18.6 µmol, 15 mol%). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged 1,2-DCB (0.63 mL). The reaction mixture was sparged with CO for approximately 10 seconds, then heated at 150 °C under a CO atmosphere for 24 h. After this time, the mixture was cooled to room temperature and concentrated *in vacuo*. The crude material was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford the product **272** (3.0 mg, 12%) as a colourless oil; υ_{max}/cm^{-1}: 3264 (br. m), 3061 (m), 2992 (m), 1618 (m), 1452 (m), 1353 (m), 1277 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (5H, m, 2 × C**8**-H, 2 × C**9**-H, C**10**-H), 7.20 (1H, m, C**3**-H), 6.14 (1H, br. s, NH), 5.60 (1H, d, *J* = 8.5 Hz, C**2**-H), 5.31 (1H, d, *J* = 8.0 Hz, C**4**-H), 4.30 (2H, d, *J* = 5.0 Hz, C**6**-H$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.7 (C**1**), 151.5 (C**5**), 144.1 (C**3**), 137.5 (C**7**), 128.4, 127.5, 127.0 (C**8**, C**9**, C**10**), 103.2 (C**2**), 87.1 (C**4**), 46.4 (C**6**); HRMS: (ESI$^+$) Calculated for $C_{12}H_{13}N_2O$: 201.1022. Found [M + H]$^+$: 201.1025.

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid



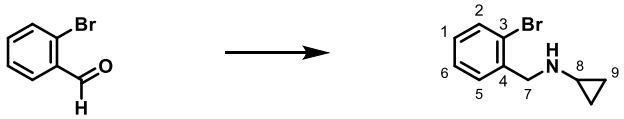
To a solution of 2-boronobenzoic acid (650 mg, 3.93 mmol) in anhydrous THF (10 mL) was added pinacol (464 mg, 3.93 mmol) and $MgSO_4$ (943 mg, 7.86 mmol). The reaction mixture was stirred at room temperature for 20 hours, then filtered and concentrated *in vacuo* to afford the title compound **416** (927 mg, 95%) as a white solid. The product was used in the following step without any further purification. ν_{max}/ cm^{-1}: 2972 (w), 1671 (s), 1340 (s), 1307 (s), 1140 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (1H, dt, *J* = 7.5, 1.0 Hz, C**2**-H), 7.55 (1H, td, *J* = 7.5 1.5 Hz, ArC-H), 7.51 – 7.40 (2H, m, 2 × ArC-H), 1.30 (12H, s, 4 × C**9**-H$_3$); ^{13}C NMR (101 MHz, DMSO-D_6): δ 169.2 (C**7**), 134.2 (C**4**), 131.5, 131.5, 128.8, 128.0 (4 × Ar-CH), 83.1 (C**8**), 24.6 (C**9**). The carbon bearing the boron substituent is not observed due to broadening. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[349]

***N*-Benzyl-*N*-cyclopropyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (275)**



To a solution of carboxylic acid **416** (250 mg, 1.01 mmol) in anhydrous CH_2Cl_2 (10 mL) was added diisopropylethylamine (0.26 mL, 1.51 mmol) and HBTU (574 mg, 1.51 mmol). The reaction mixture was stirred at room temperature for 45 minutes. A solution of amine **170a** (148 mg, 1.01 mmol) in 5 mL of CH_2Cl_2 was sparged with argon and added to the reaction mixture. The reaction mixture was stirred for an additional 16 hours and then concentrated *in vacuo*. The crude material was purified by flash column chromatography (20–40% EtOAc/hexane) to afford the title compound **275** (220 mg, 58%, 4:1 mixture of rotamers *A*:*B*) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (2H, d, *J* = 6.5 Hz, C**2**-H, *A*+*B*), 7.47 – 7.26 (16H, m, 8 × ArC-H, *A*+*B*), 4.80 (2H, s, C**8**-H_2, *A*), 4.30 (2H, s, C**8**-H_2, *B*), 2.62 (2H, tt, *J* = 7.5, 4.0 Hz, C**9**-H, *A*+*B*), 1.32 (24H, s, 4 × C**12**-H_3, *A*+*B*), 0.90 – 0.83 (4H, m, 2 × C**10**-H_2, *B*), 0.67 – 0.27 (4H, m, 2 × C**10**-H_2, *A*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2 (C**7**, *A*), 174.0 (C**7**, *B*) 143.1 (ArC, *B*), 142.5 (ArC, *A*), 138.5 (ArC, *B*), 137.4 (C**2**, *B*), 135.6 (C**2**, *A*), 130.9, 129.6, 128.7, 128.5, 128.1, 127.4, 127.1, 126.1 (12 × Ar-CH, *A*+*B*), 83.9 (C**11**, *B*), 83.3 (C**11**, *A*), 53.4 (C**8**, *B*), 51.5 (C**8**, *A*), 32.2 (C**9**, *A*), 28.3 (C**9**, *B*), 24.9 (C**12**, *A*+*B*), 9.2 (C**10**, *A*), 7.4 (C**10**, *B*). The carbon bearing the boron substituent is not observed due to broadening. ^{11}B NMR (128 MHz, $CDCl_3$): δ 28.9. HRMS: $(ESI)^+$ Calculated for $C_{23}H_{29}BNO_3$: 378.2239. Found $[M + H^+]$: 378.2237.

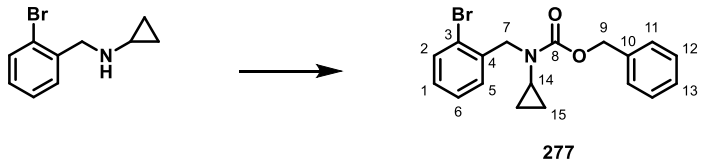
***N*-(2-Bromobenzyl)cyclopropanamine**



A solution of cyclopropylamine (0.42 mL, 6.00 mmol), 2-bromobenzaldehyde (0.58 mL, 5.00 mmol) and $NaHCO_3$ (640 mg, 7.50 mmol) in MeOH (20 mL) was heated to reflux for 24 h. The reaction mixture was cooled to 0 °C and $NaBH_4$ (231 mg, 6.25 mmol) was added portionwise over 10 minutes. The solution was warmed to room temperature and stirred for 5 hours. The reaction mixture was concentrated *in vacuo* and sat. aq. $NaHCO_3$ (25 mL) was added. The solution was extracted with CH_2Cl_2 (3 × 25 mL), the organic extracts were combined, washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (20–100% Et_2O/hexane) to afford the title compound (500 mg, 45%) as a colourless oil; ν_{max}/ cm^{-1}: 3071 (m), 2921 (w), 1468 (m), 1437 (m), 1342 (m), 1066 (s), 655 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53

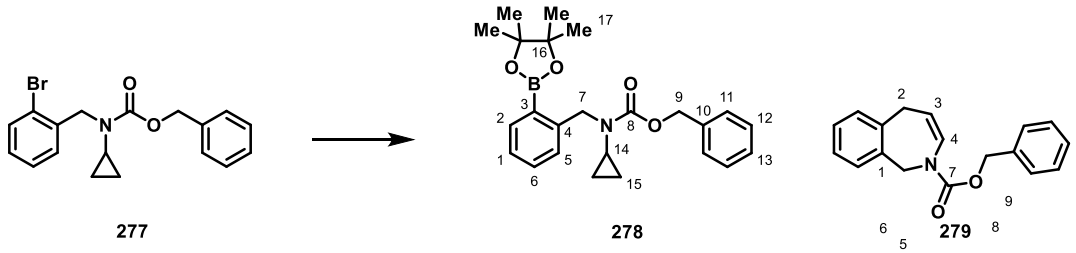
(1H, dd, *J* = 7.5, 1.5 Hz, C**2**-H), 7.35 (1H, dd, *J* = 7.5, 2.0 Hz, ArC-H), 7.27 (1H, dd, *J* = 7.5, 1.5 Hz, ArC-H), 7.11 (1H, ddd, *J* = 7.5, 2.0, 1.5 Hz, ArC-H), 3.91 (2H, s, C**7**-H_2), 2.17 – 2.03 (2H, m, C**8**-H and NH), 0.48 – 0.37 (4H, m, 2 × C**9**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.4 (C**4)**, 133.0 (C**2**), 130.8, 128.8, 127.5 (2 × Ar-CH), 124.2 (C**3**), 53.7 (C**7**), 29.8 (C**8**), 6.6 (C**9**). *The spectrscophic properties of this compound are in agreement with the literature.*[350]

Benzyl (2-bromobenzyl)(cyclopropyl)carbamate (277)



A solution of *N*-(2-bromobenzyl)cyclopropanamine (2.00 g, 7.84 mmol), K_2CO_3 (2.16 g, 15.7 mmol) and benzyl chloroformate (1.37 mL, 9.41 mmol) in toluene (30 mL) was heated at 80 °C for 24 hours. The reaction mixture was cooled to room temperature and water (30 mL) was added. The solution was extracted with EtOAc (3 × 50 mL), the organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column choromagraphy (20% Et_2O/hexane) to afford the title compound **277** (2.13 g, 76%) as a colourless oil; ν_{max}/ cm^{-1}: 2972 (w), 1598 (s), 1440 (m), 1402 (s), 1291 (m), 1139 (m), 1026 (m), 745 (s), 696 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, dd, *J* = 8.0, 1.5 Hz, C**2**-H), 7.47 – 7.16 (6H, m, 6 × ArC-H), 7.12 – 7.07 (2H, m, 2 × ArC-H), 5.17 (2H, s, C**9**-H_2), 4.58 (2H, s, C**7**-H_2), 2.64 (1H, m, s, C**14**-H), 0.79 – 0.61 (4H, m, 2 × C**15**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.1 (C**8**), 137.3, 136.7 (2 × ArC), 132.8 (C**2**), 128.5, 128.4, 127.9, 127.8, 127.8, 127.5 (6 × Ar-CH), 122.7 (ArC), 67.3 (C**9**), 52.0 (C**7**), 29.6 (C**14**), 8.01 (C**15**); HRMS: (ESI)$^+$ Calculated for $C_{18}H_{19}{}^{79}BrNO_2$: 360.0593. Found $[M + H]^+$: 360.0599.

Benzyl cyclopropyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)carbamate (278) and **benzyl 1,5-dihydro-2*H*-benzo[*c*]azepine-2-carboxylate (279)**



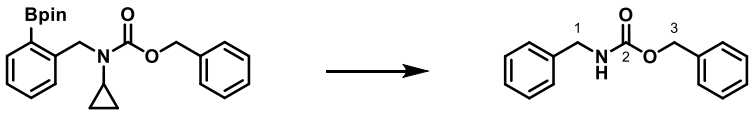
To a two-necked round-bottom flask containing Pd(dppf)Cl_2·CH_2Cl_2 (240 mg, 0.295 mmol, 5 mol%) was added bis(pinacolato)diboron (1.79 g, 7.09 mmol) and potassium acetate (1.16 g, 11.8 mmol) under nitrogen. The reagents were dissolved in anhydrous 1,4-dioxane (50 mL). A solution of aryl bromide **277** (2.12 g, 5.91 mmol) in anhydrous 1,4-dioxane (5 mL) was sparged with argon and added to the reaction mixture. The reaction mixture was heated at 70 °C for 16 hours, then cooled to room

temperature and water (50 mL) was added. The solution was extracted with EtOAc (3 × 50 mL) and the organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column choromagraphy (10–15% Et_2O/hexane) to afford the title compound **278** (1.61 g, 67%) as white solid and the title compound **279** (426 mg, 26%, 3:1 mixture of rotamers *A*:*B*) as an off-white solid.

Data for compound **277**: m.p.: 118–120 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 2977 (w), 1699 (s), 1343 (s), 1142 (s), 1056 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (1H, dd, *J* = 7.5, 1.5 Hz, C**2**-H), 7.39 – 7.03 (8H, m, C**1**-H, C**5**-H, C**6**-H, 2 × C**11**-H, 2 × C**12**-H and C**13**-H), 5.09 (2H, s, C**9**-H_2), 4.80 (2H, s, C**7**-H_2), 2.54 (1H, br. m, C**14**-H), 1.26 (12H, s, 4 × C**17**-H_3), 0.66 – 0.53 (4H, m, 2 × C**15**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.9 (C**8**), 145.3 (C**4**), 137.0 (C**10**), 136.4 (C**2**), 131.3, 128.5, 128.4, 127.8, 127.8, 125.6 (6 × Ar-CH), 83.7 (C**16**), 67.1 (C**9**), 50.7 (C**7**), 29.8 (C**14**), 25.0 (C**17**), 7.84 (C**15**). The carbon bearing the boron substituent is not observed due to line broadening. ^{11}B NMR (128 MHz, $CDCl_3$): δ 31.7. HRMS: $(ESI)^+$ Calculated for $C_{24}H_{30}BNNaO_4$: 430.2164. Found $[M + Na]^+$: 430.2164.

Data for compound **279**: m.p.: 73–75 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 2939 (w), 1702 (s), 1660 (w), 1412 (m), 1348 (m), 1232 (s), 1115 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.01 (18H, m, 9 × ArC-H, *A*+*B*), 6.67 (1H, d, *J* = 10.0 Hz, C**4**-H, *B*) 6.58 (1H, d, *J* = 10.0 Hz, C**4**-H, *A*), 5.13 (2H, s, C**8**-H_2, *B*), 5.06 (2H, s, C**8**-H_2, *A*), 4.93 – 4.84 (5H, m, C**3**-H, *B* and C**5**-H_2, *A*+*B*), 4.76 (1H, dt, *J* = 10.5, 5.5 Hz, C**3**-H, *A*), 3.50 (4H, d, *J* = 5.5, C**2**-H_2, *A*+*B*); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.7 (C**7**, *A*+*B*), 140.9 (2 signals, C**6**, *A*+*B*) 136.4, 136.2, 136.1 136.0 (C**1** and C**9**, *A*+*B*), 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 127.9, 127.5, 127.4, 127.1, 127.0, 126.1 (C**2**, *A*+*B* and 14 × Ar-CH, *A*+*B*), 107.2 (C**3**, *B*), 106.3 (C**3**, *A*), 68.0 (C**8**, *A*), 67.9 (C**8**, *B*), 49.0 (C**5**, *B*), 48.8 (C**5**, *A*), 32.3 (C**2**, *A*), 32.2 (C**2**, *B*); HRMS: $(ESI)^+$ Calculated for $C_{18}H_{18}NO_2$: 280.1332. Found $[M + H]^+$: 280.1319.

Benzyl benzylcarbamate (281)

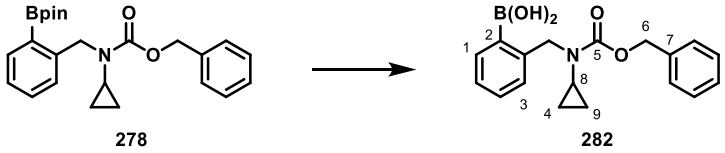


278 281

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)OH]_2$ (1.71 mg, 3.75 μmol, 3.75 mol%), P-$(4FC_6H_4)_3$ (4.74 mg, 15.0 μmol, 15 mol%) and substrate **278** (28.1 mg, 0.10 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged 1,2-DCB (1.0 mL). The reaction mixture was sparged with CO for approximately 10 seconds, then heated at 120 °C under a CO atmosphere for 72 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10–50% EtOAc/hexane) to afford the title compound **281** (10.6 mg, 44%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.25 (10H, m, 10 × ArC-H), 5.13 (2H, s, C**3**-

H$_2$), 5.05 (1H, br. s, NH), 4.38 (2H, d, *J* = 6.0 Hz, C**1**-H$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.4 (C**2**), 138.3 (ArC), 136.5 (ArC), 128.7, 128.5 (2 signals), 128.2, 127.5 (Ar-CH), 66.8 (C**3**), 45.2 (C**1**); LRMS: (ESI)$^+$ Calculated for $C_{15}H_{16}NO_2$: 241.11. Found [M + H] $^+$: 242.12. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[351]

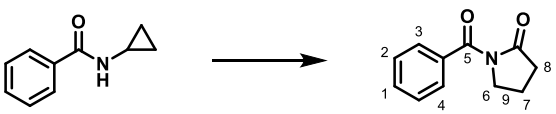
(2-((((Benzyloxy)carbonyl)(cyclopropyl)amino)methyl)phenyl)boronic acid (282)



278 282

To a solution of substrate **278** (407 mg, 1.00 mmol) in THF:H_2O (12 mL, 5:1) was added $NaIO_4$ (639 mg, 3.00 mmol). The reaction mixture was stirred at room temperature for 3 hours. After this time, 3 M aq. HCl (0.6 mL) was added and the reaction was stirred for an additional hour and then concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with water (20 mL). The aqueous portion was further extracted with EtOAc (2 × 20 mL) and the organic extracts were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column choromagraphy (20–100% EtOAc/hexane) to afford the title compound **282** (103 mg, 32%, 2:1 mixture of rotamers *A*:*B*) as white solid; m.p.: 115–118 °C (MeOH); ν_{max}/ cm^{-1}: 3356 (br. s), 3015 (w), 1573 (s), 1412 (s), 1341 (s), 1272 (s), 1139 (m); ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.38 – 7.07 (18H, m, 9 × Ar-CH, *A*+*B*), 5.10 (4H, s, C**6**-H$_2$, *A*+*B*), 4.65 (2H, s, C**4**-H$_2$, *B*), 4.50 (2H, s, C**4**-H$_2$, *A*), 2.54– 2.43 (2H, C**8**-H, *A*+*B*), 0.69 – 0.60 (8H, m, 2 × C**9**-H$_2$, *A*+*B*); ^{13}C NMR (101 MHz, methanol-D_4): δ 158.2 (C**5**, *B*), 158.0 (C**5**, *A*), 141.9 (C**3**, *B*), 140.7 (C**3**, *A*), 136.7 (2 signals, C**7**, *A*+*B*), 133.2 (C**1**, *B*), 131.5 (C**1**, *A*), 129.1, 128.7, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.1, 126.5, 126.2, 125.9 (12 × Ar-CH, *A*+*B*), 67.1 (C**6**, *A*+*B*), 51.2 (C**4**, *A*), 50.1 (C**4**, *B*), 29.4 29.0 (C**8**, *A*+*B*), 7.5 (C**15**, *A*+*B*). The carbon bearing the boron substituent is not observed due to line broadening. ^{11}B NMR (128 MHz, methanol-D_4): δ 28.7. HRMS: (ESI)$^+$ Calculated for $C_{18}H_{21}BNO_4$: 326.1561. Found [M + H] $^+$: 326.1563.

1-Benzoylpyrrolidin-2-one (174b)



171b 174b

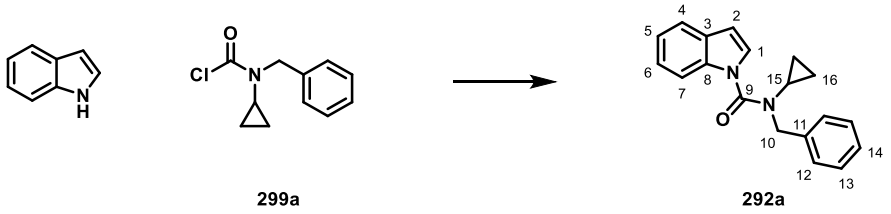
*Substrate **171a** was synthesised by M. Shaw.* An oven dried reaction tube, fitted with a magnetic stirrer, was charged with [Rh(cod)$_2$]OTf (7.02 mg, 15.0 μmol, 7.5 mol%), P(4-(F)C_6H_4)$_3$ (9.48 mg, 0.03 mmol, 22.5 mol%), 2-nitrobenzoic acid (50.1 mg, 0.3 mmol, 150 mol%) and substrate **171b** (32.2 mg, 0.20 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with argon. The reagents were

dissolved in argon sparged PhCN (2 mL). The reaction mixture was sparged with CO for approximately 10 seconds, then heated at 130 °C under a CO atmosphere for 48 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10–35 % EtOAc/pentane) to yield the title compound **174b** (11.3 mg, 30%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.57 (4H, m, 2 × C**2**-H and 2 × C**3**-H), 7.53 – 7.44 (1H, m, C**1**-H), 3.96 (2H, t, *J* = 7.0 Hz, C**6**-H_2), 2.59 (2H, t, *J* = 8.0 Hz, C**8**-H_2), 2.15 (2H, tt, *J* = 8.0, 7.0 Hz, C**7**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4 (C**9**), 170.1 (C**5**), 134.1 (C**4**), 129.8, 128.4, 127.1 (C**1**, C**2** and C**3**), 47.7 (C**6**), 33.7 (C**8**), 17.4 (C**7**). *The spectroscopic properties of this compound are in agreement with the literature.*[352]

7.5 Experimental procedures for the studies in Chapter 4

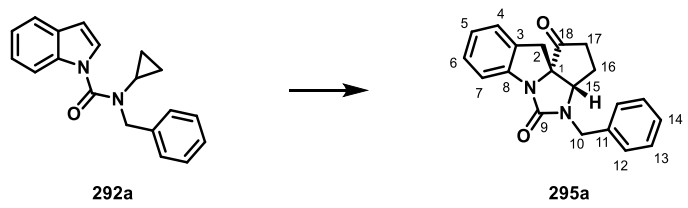
7.5.2 Synthesis of substrates and catalysis products

_N_-Benzyl-_N_-cyclopropyl-1_H_-indole-1-carboxamide (292a)



General Procedure G: Indole (400 mg, 3.40 mmol) and carbamoyl chloride **299a** (781 mg, 3.74 mmol) were employed. The crude mixture was purified by flash column chromatography (40% toluene/hexane then 100% EtOAc) to afford the title compound **292a** (897 mg, 91%) as colourless solid; m.p. 50–52 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 1673 (s), 1453 (s), 1405 (m), 1319 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, m, C**7**-H), 7.49 (1H, dd, *J* = 7.5, 1.0 Hz, C**4**-H), 7.34 (1H, d, *J* = 3.5 Hz, C**1**-H), 7.30 – 7.16 (6H, m, C**6**-H , 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.11 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 6.49 (1H, d, *J* = 3.5 Hz, C**2**-H), 4.61 (2H, s, C**10**-H_2), 2.54 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 0.63 – 0.45 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.2 (C**9**), 137.0 (C**11**), 135.7 (C**8**), 129.5 (C**3**), 128.7, 128.3 (C**12** and C**13**), 127.7 (C**14**), 125.9 (C**1**), 123.6 (C**6**), 122.0 (C**5**), 120.8 (C**4**), 113.8 (C**7**), 105.8 (C**2**), 53.3 (C**10**), 31.4 (C**15**), 9.2 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{19}N_2O$: 291.1492. Found [M + H]$^+$: 291.1493.

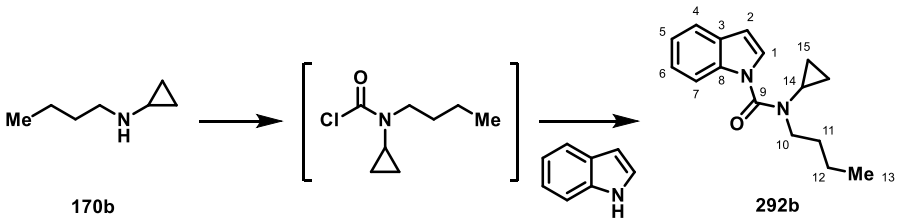
(3a*S,11a*S**)-4-Benzyl-2,3,3_a_,4-tetrahydro-11_H_-cyclopenta[4,5]imidazo[1,5-_a_]indole-1,5-dione (295a)**



292a 295a

General Procedure H: Indole **292a** (43.5 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed was employed and the reaction mixture was heated at 130 °C for 72 h. The crude mixture was purified by flash column chromatography (20% EtOAc/hexane) to yield the title compound **295a** (39.1 mg, 82%) as a colourless solid; m.p.: 126–127 °C ($CDCl_3$); ν_{max}/ cm^{-1}: 2919 (m), 1748 (s), 1710 (s), 1480 (s), 1409 (s), 1290 (s), 1158 (s); ^1H NMR (400 MHz $CDCl_3$): δ 7.50 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.40 – 7.26 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.24 – 7.17 (2H, m, C**4**-H and C**6**-H), 7.06 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 4.67 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.36 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.09 (1H, d, *J* = 5.5 Hz, C**15**-H), 3.35 (1H, d, *J* = 16.0 Hz, 1 × C**2**-H_2), 3.08 (1H, d, *J* = 16.0 Hz, 1 × C**2**-H_2), 2.62 (1H, ddd, *J* = 17.5, 13.5, 9.0 Hz, 1 × C**17**-H_2), 2.36. – 2.20 (2H, m, 1 × C**17**-H_2, 1 × C**16**-H_2), 1.86 (1H, dddd, *J* = 13.5, 7.5, 5.5, 2.0 Hz, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.3 (C**18**), 159.2 (C**9**), 142.4 (C**8**), 136.2 (C**11**), 130.1 (C**3**), 128.9, 128.2, 128.1, 128.0 (C**4**, C**12**, C**13**, C**14**), 124.7 (C**6**), 124.3 (C**5**), 116.0 (C**7**), 70.1 (C**1**), 63.8 (C**15**), 45.9 (C**10**), 35.7 (C**2**), 33.2 (C**17**), 23.3 (C**16**); HRMS: $(ESI)^+$ Calculated for $C_{20}H_{19}N_2O_2$: 319.3760. Found $[M + H]^+$: 319.1456.

***N*-Butyl-*N*-cyclopropyl-1*H*-indole-1-carboxamide (292b)**

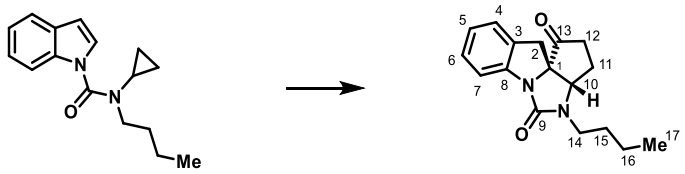


170b 292b

Pyridine (1.91 mL, 24.0 mmol) was added dropwise to a solution of triphosgene (2.24 g, 7.66 mmol) in CH_2Cl_2 (50 mL) at 0 °C. To the resulting suspension was added a solution of *N*-butylcyclopropanamine **170b** (2.26 g, 21.0 mmol) in CH_2Cl_2 (3 mL) and the resulting solution was warmed to room temperature. After 2 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with Et_2O (2 × 40 mL). The organic layers were combined and washed with 0.2 M aqueous HCl (30 mL), brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give butyl(cyclopropyl)carbamic chloride (1.98 g, 67%) as a yellow oil which was used without further purification. A flame-dried round-bottomed flask was charged with NaH (240 mg, 6.00 mmol) and this was suspended in anhydrous THF (10 mL) under nitrogen. The suspension was cooled to 0 °C and indole (351 mg, 3.00 mmol) was added portion wise over 5 minutes. The solution was warmed to room temperature and stirred for 1 hour, followed by dropwise addition of butyl(cyclopropyl)carbamic

chloride (578 mg, 3.30 mmol) in THF (7.00 mL) over 10 minutes. The solution was then stirred for 4 hours at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (10% toluene/hexane then 100% EtOAc) to afford the title compound **292b** (699 mg, 91%) as a colourless oil; ν_{max}/ cm^{-1}: 2958 (m), 1671 (s), 1524 (m), 1452 (s), 1407 (s), 1210 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H), 7.59 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz, C**4**-H), 7.41 (1H, d, *J* = 3.5 Hz, C**1**-H), 7.28 (1H, m, C**6**-H), 7.19 (1H, ddd, *J* = 8.0, 8.0, 1.0 Hz, C**5**-H), 6.57 (1H, dd, *J* = 3.5, 1.0 Hz, C**2**-H), 3.52 (2H, t, *J* = 7.0 Hz, C**10**-H_2), 2.84 (1H, tt, *J* = 7.0, 4.0 Hz, C**14**-H), 1.79 – 1.66 (2H, m, C**11**-H_2), 1.39 (2H, tt, *J* = 7.5, 7.5 Hz, C**12**-H_2), 0.94 (3H, t, *J* = 7.5 Hz, C**13**-H_3), 0.77 – 0.67 (2H, m, 1 × C**15**-H_2), 0.60 – 0.50 (2H, m, 1 × C**15**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.5 (C**9**), 135.9 (C**8**), 129.9 (C**3**), 126.2 (C**1**), 123.6 (C**6**), 121.9 (C**5**), 120.9 (C**4**), 113.9 (C**7**), 105.6 (C**2**), 49.4 (C**10**), 31.0 (C**14**), 30.2 (C**11**), 20.2 (C**12**), 13.9 (C**13**), 9.1 (C**15**); m/z (ESI^+) HRMS: Calculated for $C_{16}H_{20}N_2NaO$: 279.1468. Found $[M + Na]^+$: 279.1483.

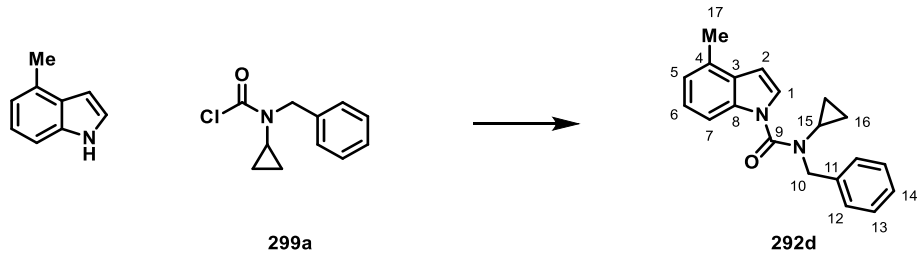
(3a*S,11a*S**)-4-Butyl-2,3,3a,4-tetrahydro-11*H*-cyclopenta[4,5]imidazo[1,5-a]indole-1,5-dione (295b)**



292b 295b

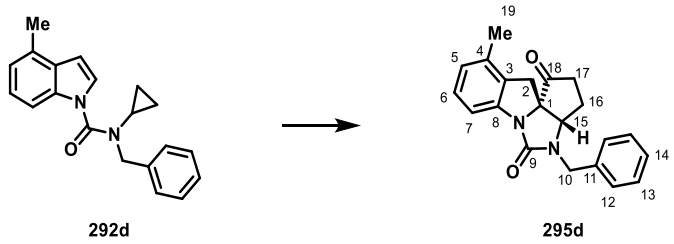
General Procedure H: Indole **292b** (38.4 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed was employed and the reaction mixture was heated at 130 °C for 72 h. The crude mixture was purified by flash column chromatography (15% EtOAc/toluene) to yield the title compound **295b** (22.6 mg, 54%) as a yellow oil; ν_{max}/ cm^{-1}: 2958 (m), 1750 (s), 1708 (s), 1480 (s), 1409 (s), 1292 (s), 1160 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H), 7.24 – 7.16 (2H, m, C**5**-H and C**6**-H), 7.04 (1H, dd, *J* = 7.5, 1.0 Hz, C**4**-H), 4.24 (1H, d, *J* = 5.5 Hz, C**10**-H), 3.48 – 3.37 (2H, m, 1 × C**2**-H_2 and 1 × C**14**-H_2), 3.22 – 3.10 (2H, m, 1 × C**2**-H_2 and 1 × C**14**-H_2), 2.67 (1H, ddd, *J* = 17.5, 13.5, 9.0 Hz, 1 × C**12**-H_2), 2.42 – 2.27 (2H, m, 1 × C**11**-H_2 and 1 × C**12**-H_2), 1.99 (1H, ddd, *J* = 14.0, 7.5, 5.5 Hz, 1 × C**11**-H_2), 1.61 – 1.45 (2H, m, C**15**-H_2), 1.39 – 1.23 (2H, m, C**16**-H_2), 0.93 (3H, t, *J* = 7.3 Hz, C**17**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4 (C**13**), 159.2 (C**9**), 142.7 (C**3**), 130.1 (C**8**), 128.1 (C**4**), 124.8 (C**5**), 124.3 (C**6**), 116.0 (C**7**), 70.2 (C**1**), 64.1 (C**10**), 41.7 (C**14**), 35.9 (C**2**), 33.3 (C**12**), 29.6 (C**15**), 23.8 (C**11**), 20.3 (C**16**), 13.9 (C**17**); HRMS: (ESI^+) Calculated for $C_{17}H_{21}N_2O_2$: 285.1598. Found $[M + H]^+$: 285.1601.

***N*-Benzyl-*N*-cyclopropyl-4-methyl-1*H*-indole-1-carboxamide (292d)**



General Procedure G: 4-Methylindole (131 mg, 1.00 mmol) and carbamoyl chloride **299a** (220 mg, 2.40 mmol) were employed. The crude mixture was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **292d** as a colourless oil (258 mg, 85%); ν_{max}/ cm^{-1}: 3027 (m), 1672 (s), 1485 (s), 1406 (s), 1273 (s), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, dd, *J* = 8.5, 1.0 Hz, C**7**-H), 7.45 (1H, d, *J* = 3.5 Hz, C**1**-H), 7.42 – 7.30 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.21 (1H, dd, *J* = 8.5, 7.5 Hz, C**6**-H), 7.03 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 6.64 (1H, d, *J* = 3.5 Hz, C**2**-H), 4.72 (2H, s, C**10**-H_2), 2.65 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 2.57 (3H, s, C**17**-H_3), 0.73 – 0.58 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.4 (C**9**), 137.1 (C**11**), 135.5 (C**8**), 130.3 (C**4**), 129.3 (C**3**), 128.9, 128.4 (C**12**, C**13**), 127.8 (C**14**), 125.5 (C**1**), 123.8 (C**6**), 122.4 (C**5**), 111.5 (C**7**), 104.3 (C**2**), 53.5 (C**10**), 31.4 (C**15**), 18.7 (C**17**), 9.2 (C**16**); HRMS: (ESI^+) Calculated for $C_{20}H_{21}N_2O$: 305.1648. Found $[M + H]^+$: 305.1649.

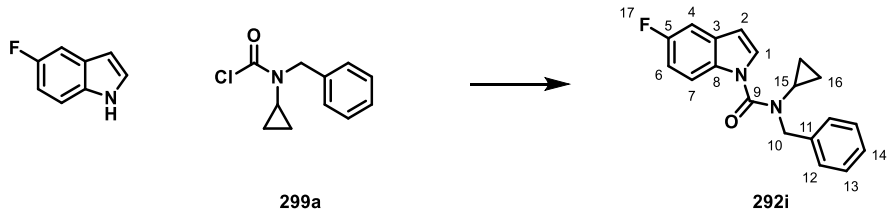
(3a*S,11a*S**)-4-Benzyl-10-methyl-2,3,3*a*,4-tetrahydro-11*H*-cyclopenta[4,5]imidazo[1,5-*a*]indole-1,5-dione (295d)**



General Procedure H: Indole **292d** (45.6 mg, 0.15 mmol)), $[Rh(cod)_2]OTf$ (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed and the reaction mixture was heated at 140 °C for 72 h. The crude mixture was purified by flash column chromatography (15% EtOAc/toluene) to yield the title compound **295d** (32.8 mg, 66%) as a yellow oil; ν_{max}/ cm^{-1}: 2914 (m), 1750 (s), 1704 (s), 1409 (s), 1288 (s), 1158 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (6H, m, C**7**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.16 (1H, dd, *J* = 7.5, 7.5 Hz, C**6**-H), 6.88 (1H, d, *J* = 7.5 Hz, C**5**-H), 4.68 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.36 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.10 (1H, d, *J* = 5.0 Hz, C**15**-H), 3.26 (1H, d, *J* = 16.0 Hz, 1 × C**2**-H_2), 2.97 (1H, d, *J* = 16.0 Hz, 1 × C**2**-H_2), 2.61 (1H, ddd, *J* = 17.5, 13.5, 9.0 Hz, 1 × C**17**-H_2), 2.37 – 2.24 (2H, m, 1 × C**16**-H_2, 1 × C**17**-H_2), 2.22 (3H, s, C**19**-H_3), 1.87 (1H, ddd, *J* = 14.0, 7.5, 5.5 Hz, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.7 (C**18**), 159.4 (C**9**), 142.1 (C**8**), 136.3

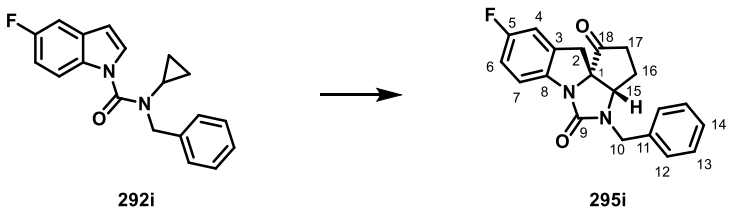
(C**11**), 134.4 (C**4**), 129.0 (C**3**), 129.0, 128.4 (C**12**, C**13**), 128.3 (C**6**), 128.0 (C**14**), 125.4 (C**5**), 113.4 (C**7**), 70.2 (C**1**), 64.2 (C**15**), 46.0 (C**10**), 34.9 (C**2**), 33.3 (C**17**), 23.3 (C**16**), 19.0 (C**19**); HRMS: (ESI$^+$) Calculated for $C_{21}H_{21}N_2O_2$: 333.1598 Found $[M + H]^+$: 333.1603.

***N*-Benzyl-*N*-cyclopropyl-5-fluoro-1*H*-indole-1-carboxamide (292i)**



General Procedure G: 5-Fluoro-1*H*-indole (142 mg, 1.05 mmol) and carbamoyl chloride **299a** (209 mg, 1.10 mmol) were employed. The crude mixture was purified by flash column chromatography (40% toluene/hexane then 100% EtOAc) to afford the title compound **292i** as a yellow oil (280 mg, 91%); ν_{max}/ cm^{-1}: 2932 (m), 1675 (s), 1468 (s), 1405 (s), 1268 (s), 1199 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (1H, m, C**4**-H), 7.48 (1H, d, *J* = 3.5 Hz, C**1**-H), 7.43 – 7.24 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.23 (1H, dd, *J* = 9.0, 2.5 Hz, C**7**-H), 7.02 (1H, dd, *J* = 9.0, 2.5 Hz, C**6**-H), 6.54 (1H, dd, *J* = 3.5, 1.0 Hz, C**2**-H), 4.70 (2H, s, C**10**-H_2), 2.63 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 0.78 – 0.49 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0 (d, *J* = 237.9 Hz, C**5**), 155.0 (C**9**), 137.0 (C**11**), 132.3 (d, *J* = 0.6 Hz, C**8**), 130.2 (d, *J* = 10.2 Hz, C**3**), 128.1, 128.4, 127.9 (C**12**, C**13** and C**14**), 127.5 (C**1**), 114.9 (d, *J* = 9.4 Hz, C**7**), 111.83 (d, *J* = 25.6 Hz, C**6**), 106.11 (d, *J* = 24.0 Hz, C**4**), 105.7 (d, *J* = 3.9 Hz, C**2**), 53.4 (C**10**), 31.6 (C**15**), 9.4 (C**16**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -121.94 (ddd, *J* = 9.0, 9.0, 4.5 Hz); HRMS: (ESI)$^+$ Calculated for $C_{19}H_{17}FN_2NaO$: 331.1217. Found $[M + Na]^+$: 331.1228.

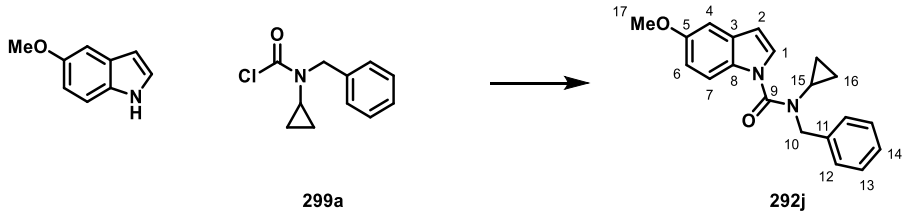
(3a*S,11a*S**)-4-Benzyl-9-fluoro-2,3,3a,4-tetrahydro-11*H*-cyclopenta[4,5]imidazo[1,5-*a*]indole-1,5-dione (295i)**



General Procedure H: Indole **292i** (46.2 mg, 0.15 mmol)), $[Rh(cod)_2]OTf$ (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed and the reaction mixture was heated at 130 °C for 72 h. The crude mixture was purified by flash column chromatography (10% EtOAc/toluene) to yield the title compound **295i** (27.0 mg, 54%) as a colourless oil; ν_{max}/ cm^{-1}: 2922 (m), 1751 (s), 1710 (s), 1485 (s), 1408 (s), 1308 (s), 1261 (s), 1160 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (1H, dd, *J* = 8.5, 4.5 Hz, C**7**-H), 7.40 – 7.27 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.96 – 6.88 (2H, m, C**4**-H and C**6**-H), 4.68 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.36 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.09 (1H, d, *J* = 5.5 Hz, 1 ×

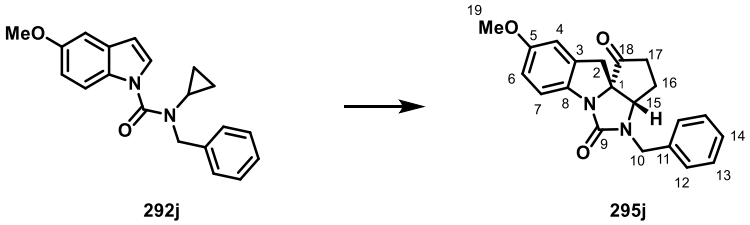
C**15**-H), 3.34 (1H, d, *J* = 16.5 Hz, 1 × C**2**-H$_2$), 3.07 (1H, dd, *J* = 16.5, 1.0 Hz, 1 × C**2**-H$_2$), 2.64 (1H, ddd, *J* = 17.5, 13.5, 9.0 Hz, 1 × C**17**-H$_2$), 2.35 – 2.19 (2H, m, 1 × C**16**-H$_2$, 1 × C**17**-H$_2$), 1.87 (1H, m, 1 × C**16**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 211.8 (C**18**), 160.4 (d, *J* = 241.8 Hz, C**5**), 159.2 (C**9**), 138.3 (d, *J* = 1.9 Hz, C**3**), 136.2 (C**11**), 132.10 (d, *J* = 8.7 Hz, C**8**), 129.0, 128.4 (C**12**, C**13**), 128.1 (C**14**), 116.8 (d, *J* = 8.8 Hz, C**7**), 114.7 (d, *J* = 23.6 Hz, C**6**), 112.1 (d, *J* = 24.2 Hz, C**4**), 70.6 **(**C**1**), 63.5 (C**15**), 46.1 (C**10**), 35.7 (d, *J* = 2.0 Hz, C**2**), 33.2 (C**17**), 23.5 (C**16**); ^{19}F NMR (377 MHz, $CDCl_3$): δ -119.1 (ddd, *J* = 8.6, 8.6, 4.6 Hz); HRMS: (ESI$^+$) Calculated for $C_{20}H_{17}FN_2NaO_2$: 359.1184. Found $[M + Na]^+$: 359.1184.

***N*-Benzyl-*N*-cyclopropyl-5-methoxy-1*H*-indole-1-carboxamide (292j)**



General Procedure G: 5-Methoxy-1*H*-indole (147 mg, 1.00 mmol) and carbamoyl chloride **299a** (220 mg, 1.10 mmol) were employed. The crude mixture was purified by flash column chromatography (90% toluene/hexane then 100% EtOAc) to afford the title compound **292j** (280 mg, 91%) as a light brown oil; ν_{max}/ cm^{-1}: 2940 9m), 1673 (s), 1473 (s), 1406 (s), 1266 (s), 1149 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (1H, d, *J* = 9.0 Hz , C**7**-H), 7.42 (1H, d, *J* = 3.5 Hz, C**1**-H), 7.40 – 7.28 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.05 (1H, d, *J* = 2.5 Hz, C**4**-H), 6.92 (1H, dd, *J* = 9.0, 2.5 Hz, C**6**-H), 6.50 (1H, d, *J* = 3.5 Hz, C**2**-H), 4.69 (2H, s, C**10**-H$_2$), 3.85 (3H, s, C**17**-H$_3$), 2.62 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 0.72 – 0.55 (4H, m, 2 × C**16**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.5, 155.3 (C**5** and C**9**), 137.0 (C**11**), 130.6, 130.2 (C**3**, C**8**), 128.8, 128.3 (C**12**, C**13)**, 127.7 (C**14**), 126.5 (C**1**), 114.7 (C**7**), 113.0 (C**6**), 105.6 (C**2**), 103.0 (C**4**), 55.7 (C**17**), 53.3 (C**10**), 31.4 (C**15**), 9.2 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{20}N_2NaO_2$: 343.1417 Found $[M + Na]^+$: 343.1417.

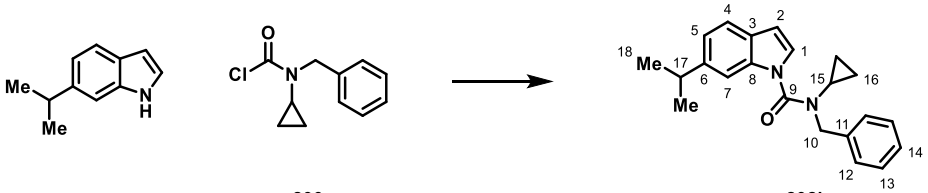
(3a*S,11a*S**)-4-Benzyl-9-methoxy-2,3,3a,4-tetrahydro-11*H* cyclopenta[4,5]imidazo[1,5-*a*]indole-1,5-dione (295j)**



General Procedure H: Indole **292j** (48.0 mg, 0.15 mmol), [Rh(cod)$_2$]OTf (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed and the reaction mixture was heated at 130 °C for 72 h. The crude mixture was purified by flash column chromatography (15% EtOAc/toluene) to yield the title

compound **295j** (34.3 mg, 66%) as a colourless oil; ν_{max}/ cm^{-1}: 2921 (m), 1750 (s), 1709 (s), 1496 (s), 1406 (s), 1155 (s), 1027 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (1H, d, *J* = 8.5 Hz, C**7**-H), 7.38 – 7.12 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.81 – 6.74 (2H, m, C**4**-H and C**6**-H), 4.69 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.35 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.08 (1H, d, *J* = 5.5 Hz, C**15**-H), 3.77 (3H, s, C**19**-H_3), 3.32 (1H, d, *J* = 16.0 Hz, 1 × C**2**-H_2), 3.06 (1H, d, *J* = 16.0 Hz, 1 × C**2**-H_2), 2.66 (1H, ddd, *J* = 17.5, 13.5, 9.5 Hz, 1 × C**17**-H_2), 2.31 (1H, m, 1 × C**17**-H_2), 2.21 (1H, m, 1 × C**16**-H_2), 1.86 (1H, m, 1 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.0 (C**18**), 159.7 (C**9**), 157.4 (C**5**), 136.3 (C**11**), 135.8 (C**3**), 131.7 (C**8**), 129.0, 128.2 (C**12**, C**13**), 128.0 (C**14**), 116.7 (C**7**), 113.1 (C**6**), 111.0 (C**4**), 70.6 (C**1**), 63.5 (C**15**), 55.9 (C**19**), 46.0 (C**10**), 35.9 (C**2**), 33.3 (C**17**), 23.6 (C**16**); HRMS: (ESI$^+$) Calculated for $C_{21}H_{21}N_2O_3$: 349.1547. Found [M + H]$^+$: 349.1551.

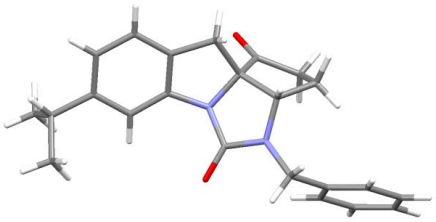
***N*-Benzyl-*N*-cyclopropyl-6-isopropyl-1*H*-indole-1-carboxamide (292k)**



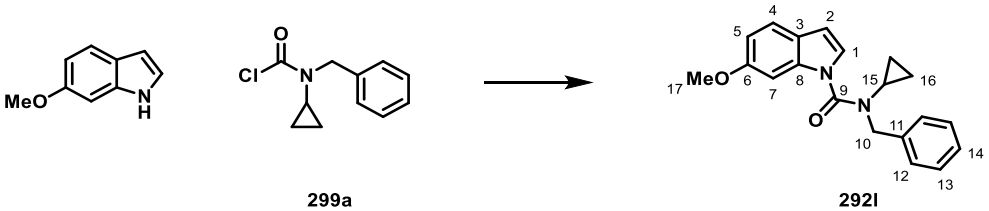
General Procedure G: 6-Isopropyl-*1H*-indole (318 mg, 2.00 mmol) and carbamoyl chloride **299a** (502 mg, 2.40 mmol) were employed. The crude mixture was purified by flash column chromatography (90% toluene/hexane) to afford the title compound **292k** as a brown oil (610 mg, 92%); ν_{max}/ cm^{-1}: 2958 (m), 1671 (s), 1437 (s), 1404 (s), 1318 (s), 1210 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, dd, *J* = 1.5, 1.0 Hz, C**7**-H), 7.49 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.40 – 7.29 (6H, m, C**1**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.10 (1H, dd, *J* = 8.0, 1.5 Hz, C**5**-H), 6.53 (1H, d, *J* = 3.5 Hz, C**2**-H), 4.71 (2H, s, C**10**-H_2), 3.01 (1H, hept, *J* = 7.0 Hz, C**17**-H), 2.62 (1H, tt, *J* = 6.5, 4.0 Hz, C**15**-H), 1.28 (6H, d, *J* = 7.0 Hz, 2 × C**18**-H_3), 0.74 – 0.53 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): 155.4 (C**9**), 145.1 (C**6**), 137.2 (C**11**), 136.2 (C**8**), 128.9, 128.5, 127.9 (C**12**, C**13**, and C**14**), 127.8 (C**3**), 125.6 (C**1**), 121.4 (C**5**), 120.6 (C**4**), 111.5 (C**7**), 105.8 (C**2**), 53.4 (C**10**), 34.6 (C**17**), 31.6 (C**15**), 24.6 (C**18**), 9.4 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{22}H_{24}N_2NaO$: 355.1781. Found [M + Na]$^+$: 355.1791.

(3a*S,11a*S**)-4-Benzyl-8-isopropyl-2,3,3a,4-tetrahydro-11*H*-cyclopenta[4,5]imidazo[1,5-*a*]indole-1,5-dione (295k)**

General Procedure H: Indole **292k** (50.0 mg, 0.15 mmol), $[Rh(cod)_2]OTf$ (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed and the reaction mixture was heated at 130 °C for 72 h. The crude mixture was purified by flash column chromatography (15% EtOAc/toluene) to yield the title compound **295k** (45.0 mg, 83%) as a colourless solid; m.p.: 186–189 °C (EtOAc/petroleum ether); ν_{max}/ cm^{-1}: 2956 (m), 1751 (s), 1698 (s), 1493 (s), 1410 (s), 1286 (s), 1153 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (1H, d, *J* = 1.5 Hz, C**7**-H), 7.38 – 7.26 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.11 (1H, dd, *J* = 7.5, 1.0 Hz, C**4**-H), 6.94 (1H, dd, *J* = 7.5, 1.5 Hz, C**5**-H), 4.63 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.40 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.09 (1H, d, *J* = 5.0 Hz, C**15**-H), 3.30 (1H, d, *J* = 16.0, 1 × C**2**-H_2), 3.05 (1H, d, *J* = 16.0 Hz, 1 × C**2**-H_2), 2.93 (1H, hept, *J* = 7.0 Hz, C**19**-H), 2.59 (1H, ddd, *J* = 17.5, 13.5, 9.0 Hz, 1 × C**17**-H_2), 2.38 – 2.16 (2H, m, 1 × C**17**-H_2 and 1 × C**16**-H_2), 1.85 (1H, ddd, *J* = 14.5, 7.5, 5.5 Hz, 1 × C**16**-H_2), 1.26 (6H, d, *J* = 7.0 Hz, 2 × C**20**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.7 (C**18**), 159.3 (C**9**), 149.5 (C**6**), 142.5 (C**8**), 136.4 (C**11**), 129.0, 128.3 (C**12**, C**13**), 128.0 (C**14**), 127.5 (C**3**), 124.5 (C**4**), 122.5 (C**5**), 114.2 (C**7**), 70.6 (C**1**), 64.1 (C**15**), 46.1 (C**10**), 35.6 (C**2**), 34.3 (C**19**), 33.3 (C**17**), 24.4 (C**20**), 24.0 (C**20**), 23.4 (C**16**); m/z (ESI^+) HRMS: Calculated for $C_{23}H_{25}N_2O_2$: 361.1911. Found $[M + H]^+$: 361.1921. *The structure of this compound was determined unambiguously by X-ray crystallography.*



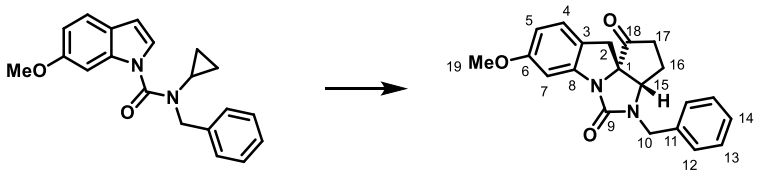
***N*-Benzyl-*N*-cyclopropyl-6-methoxy-1*H*-indole-1-carboxamide (292l)**



General Procedure G: 6-Methoxy-*1H*-indole (147 mg, 1.00 mmol) and carbamoyl chloride **299a** (220 mg, 1.05 mmol) were employed. The crude mixture was purified by flash column chromatography (90% toluene/hexane then 100% EtOAc) to afford the title compound **292l** (231 mg, 73%) as a light brown oil; ν_{max}/ cm^{-1}: 2925 (m), 1676 (s), 1612 (s), 1486 (s), 1407 (s), 1227 (s), 1227 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.37 – 7.36 (4H, m, 2 × C**12**-H and 2 × C**13**-H), 7.34 – 7.30 (3H, m, C**1**-H, C**7**-H and C**14**-H), 6.85 (1H, dd, *J* = 8.5, 2.5 Hz, C**5**-H), 6.50 (1H, d, *J* = 3.5, Hz, C**2**-

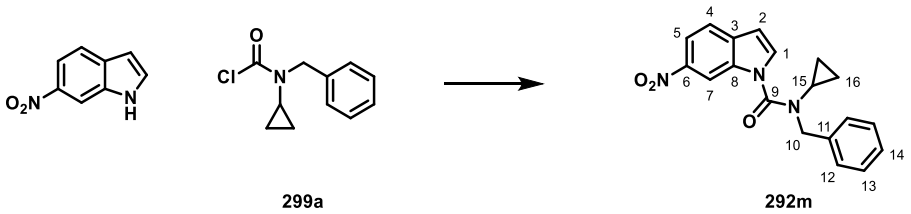
H), 4.71 (2H, s, C**10**-H$_2$), 3.81 (3H, s, C**17**-H$_3$), 2.63 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 0.72 – 0.56 (4H, m, 2 × C**16**-H$_2$): ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.4 (C**6**), 155.3 (C**9**), 137.0 (C**11**), 136.7 (C**8**), 128.8, 128.4 (C**12**, C**13**), 127.8 (C**14**), 124.6 (C**1**), 123.3 (C**3**), 121.2 (C**4**), 112.0 (C**5**), 105.7 (C**2**), 97.6 (C**7**), 55.6 (C**17**), 53.2 (C**10**), 31.4 (C**15**) 9.2 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{20}N_2NaO_2$: 343.1417. Found [M + Na]$^+$: 343.1417.

(3a*S,11a*S**)-4-Benzyl-8-methoxy-2,3,3a,4-tetrahydro-11*H*-cyclopenta[4,5]imidazo[1,5-*a*]indole-1,5-dione (295l)**



General Procedure H: Indole **292l** (48.0 mg, 0.15 mmol)), [Rh(cod)$_2$]OTf (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed and the reaction mixture was heated at 130 °C for 72 h. The crude mixture was purified by flash column chromatography (15% EtOAc/toluene) to afford the title compound **295l** (15.6 mg, 29%) as a colourless oil; ν_{max}/ cm^{-1}: 2921 9m), 1749 (s), 1708 (s), 1617 (s), 1485 (s), 1406 (s), 1309 (s), 1287 (s), 1155 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.27 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 7.11 (1H, d, *J* = 2.5 Hz, C**7**-H), 7.05 (1H, d, *J* = 8.5 Hz, C**4**-H), 6.62 (1H, dd, *J* = 8.5, 2.5 Hz, C**5**-H), 4.67 (1H, d, *J* = 15.5 Hz, 1 × C**10**-H$_2$), 4.37 (1H, d, *J* = 15.5 Hz, 1 × C**10**-H$_2$), 4.09 (1H, d, *J* = 5.5 Hz, 1 × C**15**-H), 3.82 (3H, s, C**19**-H$_3$), 3.26 (1H, d, *J* = 15.5 Hz, 1 × C**2**-H$_2$), 3.02 (1H, d, *J* = 15.5 Hz, 1 × C**2**-H$_2$), 2.59 (1H, ddd, *J* = 18.0, 13.5, 9.0 Hz, 1 × C**17**-H$_2$), 2.36 – 2.20 (2H, m, 1 × C**17**-H$_2$, 1 × C**16**-H$_2$), 1.87 (1H, dddd, *J* = 13.5, 8.0, 5.0, 2.5 Hz, 1 × C**16**-H$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 212.5 (C**18**), 160.1 (C**6**), 159.1 (C**9**), 143.5 (C**8**), 136.2 (C**11**), 128.9, 128.2 (C**12**, C**13**), 127.9 (C**14**), 124.9 (C**4**), 121.6 (C**3**), 110.8 (C**5**), 101.6 (C**7**), 70.9 (C**1**), 63.9 (C**15**), 55.6 (C**19**), 45.9 (C**10**), 35.1 (C**2**), 33.2 (C**17**), 23.2 (C**16**); HRMS: (ESI$^+$) Calculated for $C_{21}H_{20}N_2N_aO_3$: 371.1366. Found [M + Na]$^+$: 371.1370.

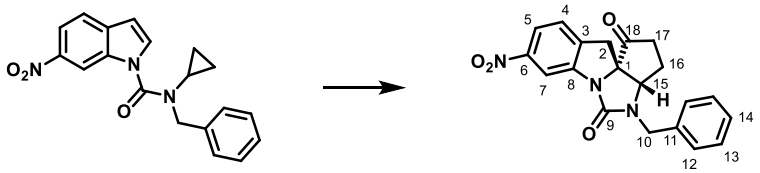
***N*-Benzyl-*N*-cyclopropyl-6-nitro-1*H*-indole-1-carboxamide (292m)**



General Procedure G: 6-Nitro-*1H*-indole (330 mg, 2.00 mmol) and carbamoyl chloride **299a** (502 mg, 2.40 mmol) were employed. The crude mixture was purified by flash column chromatography (15% EtOAc/hexane) to afford the title compound **292m** as a yellow solid (599 mg, 89%); m.p; 134–134 °C

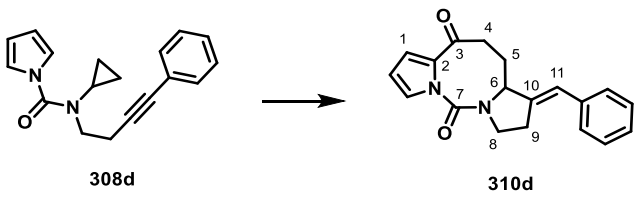
($CHCl_3$); ν_{max}/ cm^{-1}: 3132 (m), 1669 (s), 1519 (s), 1499 (s), 1413 (s), 1333 (s), 1313 (s), 1255 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.72 (1H, d, *J* = 2.0 Hz, C**7**-H), 8.11 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 7.71 (1H, d, *J* = 3.5, C**1**-H), 7.66 (1H, dd, *J* = 8.5, 1.0 Hz, C**4**-H), 7.45 – 7.31 (5H, m, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 6.69 (1H, dd, *J* = 3.5, 1.0 Hz, C**2**-H), 4.75 (2H, s, C**10**-H_2), 2.67 (1H, tt, *J* = 6.5, 3.5 Hz, C**15**-H), 0.76 – 0.50 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.9 (C**9**), 144.7 (C**6**), 136.6 (C**11**), 134.6 (C**8**), 134.2 (C**3**), 131.1 (C**1**), 129.1, 128.5 (C**12**, C**13**), 128.2 (C**14**), 121.0 (C**4**), 117.5 (C**5**), 110.7 (C**7**), 105.8 (C**2**), 53.4 (C**10**), 31.8 (C**15**), 9.5 (C**16**); HRMS: $(ESI)^+$ Calculated for $C_{19}H_{17}N_3NaO_3$: 358.1162. Found $[M + Na]^+$: 358.1174.

(3a*S,11a*S**)-4-Benzyl-8-nitro-2,3,3*a*,4-tetrahydro-11*H*-cyclopenta[4,5]imidazo[1,5-*a*]indole-1,5-dione (295m)**



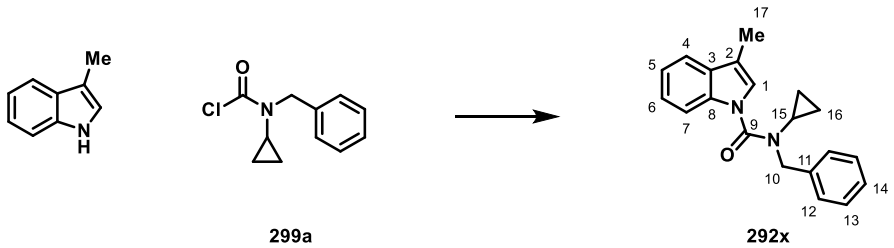
General Procedure H: Indole **292m** (50.3 mg, 0.15 mmol)), $[Rh(cod)_2]OTf$ (5.28 mg, 7.5 mol%) and anhydrous 1,2-DCB (1.50 mL) were employed and the reaction mixture was heated at 130 °C for 72 h. The crude mixture was purified by flash column chromatography (10% EtOAc/toluene) to afford the title compound **295m** (9.8 mg, 18%) as a yellow oil; ν_{max}/ cm^{-1}: 2921 (m), 1754 (s), 1714 (s), 1523 (s), 1410 (s), 1344 (s), 1215 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (1H, d, *J* = 2.0 Hz, C**7**-H), 7.97 (1H, dd, *J* = 8.5, 2.0 Hz, C**5**-H), 7.37 – 7.27 (6H, m, C**4**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 4.72 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.36 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H_2), 4.14 (1H, d, *J* = 5.5 Hz, C**15**-H), 3.44 (1H, d, *J* = 17.0 Hz, 1 × C**2**-H_2), 3.15 (1H, dd, *J* = 17.0, 1.0 Hz, 1 × C**2**-H_2), 2.65 (1H, ddd, *J* = 18.0, 13.5, 9.0 Hz, 1 × C**17**-H_2), 2.42 – 2.25 (2H, m, 1 × C**16**-H_2, 1 × C**17**-H_2), 1.91 (1H, ddd, *J* = 14.0, 7.5, 5.5 Hz, 1 × C**16**-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 211.9 (C**18**), 158.3 (C**9**), 148.7 (C**6**), 143.5 (C**8**), 137.9 (C**3**), 135.8 (C**11**), 129.2 (C**13**), 128.3 (C**12**), 128.3 (C**14**), 125.0 (C**4**), 120.2 (C**5**), 111.2 (C**7**), 70.6 (C**1**), 63.6 (C**15**), 46.2 (C**10**), 35.6 (C**2**), 33.1 (C**17**), 23.4 (C**16**) HRMS: (ESI^+) Calculated for $C_{20}H_{18}N_3O_4$: 364.1292 Found $[M + H]^+$: 364.1290.

(*E*)-7-Benzylidene-5,6,6a,7,8,9-hexahydro-4*H*,11*H*-dipyrrolo[1,2-c:2',1'-*h*][1,3]diazocine-4,11-dione (310d)



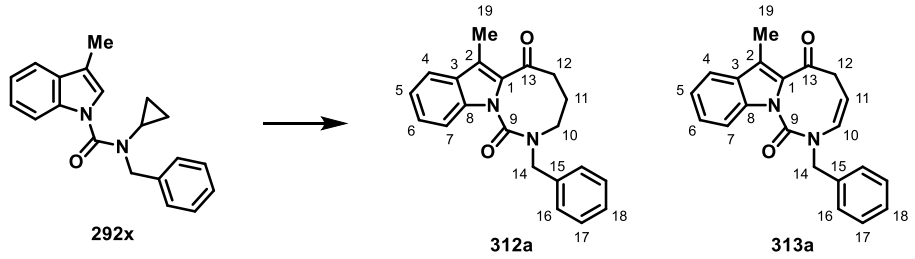
*Substrate **308d** was synthesised by G.-W. Wang.* An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (3.51 mg, 7.5 × 10^{-3} mmol, 7.5 mol%), 4-(dimethylamino)benzoic acid (2.47 mg, 15.0 μmol, 15 mol%l), tris(3,5-dimethylphenyl)phosphine (5.19 mg, 15.0 μmol, 15 mol%) Na_2SO_4 (14.2 mg, 0.1 mmol, 100 mol%) and substrate **308a** (27.8 mg, 0.10 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (1.0 mL) was added by syringe. The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The reaction mixture was heated at 130 °C for 72 hours. The mixture was cooled to room temperature, concentrated *in vacuo* and the crude residue was purified by flash column chromatography (10% EtOAc/Hex) to yield the title compound **310d** (25.9 mg, 82%) as a colourless oil; ν_{max} / cm^{-1}: 2923 (m), 1681 (s), 1654 (s), 1434 (s), 1398 (s), 1068 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, dd, *J* = 3.0, 2.0 Hz, 1 × ArC-H), 7.29 – 7.27 (2H, m, C**1**-H and 1 × ArC-H), 7.19 – 7.15 (4H, m, 4 × ArC-H), 6.27 – 6.23 (2H, m, C**11**-H and 1 × ArC-H), 4.52 (1H, dd, *J* = 13.0, 4.5 Hz, C**6**-H), 4.23 (1H, ddd, *J* = 12.5, 8.5, 6.0 Hz, 1 × C**8**-H_2), 3.67 (1H, m, 1 × C**8**-H_2), 2.94 – 2.85 (3H, m, 1 × C**4**-H_2, C**9**-H_2), 2.56 (1H, ddd, *J* = 12.5, 4.0, 3.0 Hz, 1 × C**4**-H_2), 2.10 (1H, m, 1 × C**5**-H_2), 1.93 (1H, m, 1 × C**5**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.8 (C**3**), 150.6 (C**7**), 139.8 (C**10**), 136.2 (ArC), 134.4 (C**2**) 130.1 (ArC), 128.5 (ArC-H), 128.3 (ArC-H), 127.3 (ArC-H), 123.3 (C**11**), 121.0 (C**1**), 110.7 (ArC-H), 61.8 (C**6**), 46.1 (C**8**), 37.1 (C**4**), 33.9 (C**5**), 26.7 (C**9**); HRMS: (ESI^+) Calculated for $C_{19}H_{19}N_2O_2$: 307.1441. Found $[M+H]^+$: 307.1441.

***N*-Benzyl-*N*-cyclopropyl-3-methyl-1*H*-indole-1-carboxamide (292x)**



General Procedure G: 3-Methyl-*1H*-indole (551 mg, 4.20 mmol) and carbamoyl chloride **299a** (836 mg, 4.00 mmol) were employed. The crude mixture was purified by flash column chromatography (10% toluene/petroleum ether) to afford the title compound **292x** as a yellow oil (1.15mg, 95% yield); ν_{max}/ cm^{-1}: 3028 (m), 1671 (s), 1454 (s), 1405 (s), 1335 (s), 1223 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.52 (1H, m, C**4**-H), 7.41 – 7.10 (8H, m, C**1**-H, C**5**-H, C**6**-H, 2 × C**12**-H, 2 × C**13**-H and C**14**-H), 4.67 (2H, s, C**10**-H_2), 2.61 (2H, tt, *J* = 6.5, 3.5 Hz, C**15**-H), 2.29 (3H, s, C**17**-H_3), 0.74 – 0.53 (4H, m, 2 × C**16**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.5 (C**9**), 137.3 (C**11**), 136.2 (C**8**), 130.6 (C**3**), 128.9, 128.5 (C**12**, C**13**), 127.8 (C**14**), 123.8 (C**6**), 123.2 (C**1**), 121.8 (C**5**), 119.0 (C**4**), 115.2 (C**2**), 114.1 (C**7**), 53.6 (C**10**), 31.3 (C**15**), 9.9 (C**17**), 9.3 (C**16**); HRMS: $(ESI)^+$ Calculated for $C_{20}H_{21}N_2NaO$: 327.1468. Found $[M + Na]^+$: 327.1475.

2-Benzyl-7-methyl-2,3,4,5-tetrahydro-[1,3]diazocino[1,8-*a*]indole-1,6-dione (312a) and **(*Z*)-2-Benzyl-7-methyl-2,5-dihydro-[1,3]diazocino[1,8-*a*]indole-1,6-dione (313a)**

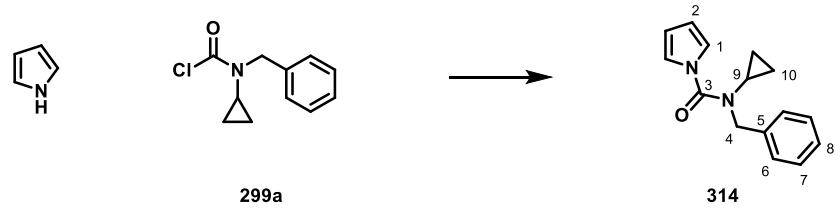


An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (3.51 mg, 7.5 μmol, 7.5 mol%), COD (4 μL, 30 μmol, 30 mol%), and indole substrate **292x** (30.4 mg, 0.10 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged 1,2-DCB (1.0 mL). The reaction mixture was sparged with CO for approximately 10 seconds, then heated at 130 °C under a CO atmosphere for 72 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (5–20% EtOAc/pentane) to afford the title compound **312a** (9.0 mg, 27%) as a colourless solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 3:1 (**312a**:**313a**) mixture of products. The minor product **313a** was not isolated.

Data for major compound **312a**: ν_{max}/ cm^{-1}: 3044 (m), 2982 (m), 1687 (s), 1653 (s), 1519 (s), 1429 (s), 1280 (s); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 7.76 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.61 (1H, d, *J* = 8.5 Hz, C**4**-H), 7.49 – 7.32 (6H, m, C**6**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.25 (1H, dd, *J* = 8.5, 7.5 Hz, C**5**-H), 4.80 (2H, s, C**14**-H_2), 3.36 (2H, t, *J* = 6.0 Hz, C**10**-H_2), 2.73 (2H, t, *J* = 6.5 Hz, C**12**-H_2), 2.60 (3H, s, C**19**-H_3), 2.00 (2H, tt, *J* = 6.5, 6.0 Hz, C**11**-H_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.7 (C**13**), 154.3 (C**9**), 138.3 (C**8**), 136.2 (C**15**), 133.5 (C**1**), 129.1, 128.4, 128.2 (2 signals), 128.1 (C**3**, C**6**, C**16**, C**17** and C**18**), 127.2 (C**2**), 122.2 (C**5**), 121.0 (C**4**), 114.7 (C**7**), 50.0 (C**14**), 44.1 (C**10**), 37.8 (C**12**), 24.4 (C**11**), 12.1 (C**19**); ^{13}C NMR (126 MHz, DMSO-d_6, 100 °C): δ 192.0 (C**13**), 152.9 (C**9**), 136.8 (C**8**), 136.3 (C**15**), 132.4 (C**1**), 128.1, 127.4, 127.4, 127.0, 126.7 (C**3**, C**6**, C**16**, C**17** and C**18**), 123.6 (C**2**), 121.2 (C**5**), 120.1 (C**4**), 113.5 (C**7**), 49.2 (C**14**), 44.0 (C**10**), 37.1 (C**12**), 23.3 (C**11**), 10.5 (C**19**); HRMS: (ESI)$^+$ Calculated for $C_{21}H_{21}N_2O_2$: 333.1598. Found [M + H] $^+$: 333.1602. *A ^{1}H NMR spectrum was recorded at 100 °C in DMSO-d_6 because at room temperature slow conformational interconversion gave a broad spectrum.*

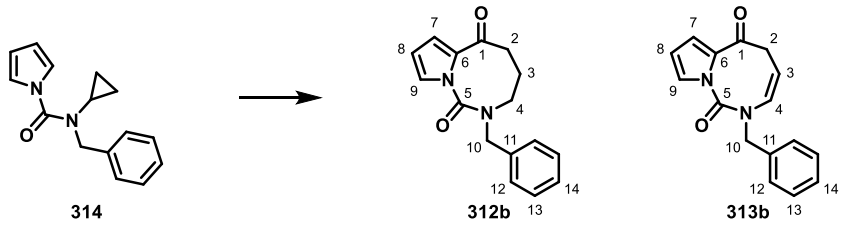
Data for minor compound **313a**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07 (1H, dt, *J* = 7.0, 1.0 Hz, C**10**-H), 5.69 (1H, td, *J* = 8.0, 7.0 Hz, C**11**-H).

***N*-Benzyl-*N*-cyclopropyl-1*H*-pyrrole-1-carboxamide (314)**



General Procedure G: 1*H*-Pyrrole (0.69 mL, 10.0 mmol) and carbamoyl chloride **299a** (313 mg. 15.0 mmol) were employed. The crude mixture was purified by flash column chromatography (10% EtOAc/hexane) to afford the title compound **314** (2.08 g, 87%) as a yellow oil; ν_{max}/ cm^{-1}: 2971 (m), 2900 (m), 1671 (s), 1412 (s), 1386 (s), 1291 (s), 1073 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (5H, m, 2 × C**6**-H, 2 × C**7**-H, C**8**-H), 7.20 (2H, d, *J* = 2.0 Hz, 2 × C**1**-H), 6.23 (2H, d, *J* = 2.0 Hz, 2 × C**2**-H), 4.69 (2H, s, C**4**-H_2), 2.64 (1H, tt, *J* = 7.0, 4.0 Hz, C**9**-H), 0.78 – 0.55 (4H, m, 2 × C**10**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7 (C**3**), 137.03 (C**5**), 128.7, 128.2 (C**6**, C**7**), 127.6 (C**8**), 120.6 (C**1**), 110.5 (C**2**), 53.2 (C**4**), 31.7 (C**9**), 9.6 (C**10**); HRMS: (ESI$^+$) Calculated for $C_{15}H_{17}N_2O$: 241.1335. Found $[M + H]^+$: 241.1344.

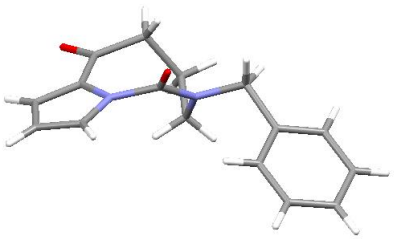
2-Benzyl-2,3,4,5-tetrahydropyrrolo[1,2-*c*][1,3]diazocine-1,6-dione (312b) and **(*Z*)-2-Benzyl-2,5-dihydropyrrolo[1,2-*c*][1,3]diazocine-1,6-dione (313b)**



An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (3.5 mg, 7.5 µmol, 7.5 mol%), COD (4 µL, 30 µmol, 30 mol%), and pyrrole substrate **314** (24.0 mg, 0.10 mmol, 100 mol%). The tube was fitted with a rubber septum and purged with argon. The reagents were dissolved in argon sparged 1,2-DCB (1.0 mL). The reaction mixture was sparged with CO for approximately 10 seconds, then heated at 130 °C under a CO atmosphere for 72 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10–30% EtOAc/pentane) to afford the title compounds **312b** (13.1 mg, 49%) as a colourless solid and **313b** (4.3 mg, 16%) as a colourless solid.

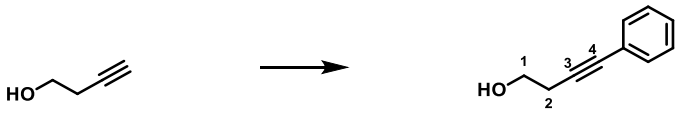
Data for major product **312b**: m.p.: 97–98 °C (pentane/EtOAc); ν_{max}/ cm^{-1}: 2928 (m), 1684 (s), 1654 (s), 1434 (s), 1418 (s), 1283 (s), 1139 (s); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 7.47 – 7.33 (6H, m, C**9**-H, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 7.08 (1H, dd, *J* = 3.5, 2.0 Hz, ArC-H), 6.38 – 6.32 (1H, m, ArC-H, 4.75 (2H, s, C**10**-H_2), 3.38 (2H, t, *J* = 6.5 Hz, C**4**-H_2), 2.60 (2H, t, *J* = 6.5 Hz, C**2**-H_2), 1.92 (2H, tt, *J* = 6.5, 6.5 Hz, C**3**-H_2); ^{1}H NMR (301 MHz, $CDCl_3$, - 50 °C): δ 7.49 (1H, dd, *J* = 3.0, 2.0 Hz, ArC-

H), 7.40 – 7.34 (5H, m, ArC-H), 7.24 (1H, m, ArC-H), 6.35 (1H, dd, *J* = 5.0, 3.0 Hz, ArC-H), 5.32 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 4.19 (1H, d, *J* = 14.5 Hz, 1 × C**10**-H_2), 3.61 (1H, ddd, *J* = 15.0, 3.0, 3.0 Hz, 1 × C**4**-H_2), 3.25 (1H, ddd, *J* = 15.0, 5.0, 5.0 Hz, 1 × C**2**-H_2), 2.91 (1H, ddd, *J* = 13.0, 5.0, 5.0 Hz, 1 × C**4**-H_2), 2.59 (1H, ddd, *J* = 12.0, 3.0, 3.0 Hz, 1 × C**2**-H_2), 2.15 (1H, m, 1 × C**3**-H_2), 1.86 (1H, m, 1 × C**3**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.6 (C**1**), 153.7 (C**5**), 135.8 (ArC), 135.2 (ArC), 130.3 (Ar-CH), 128.9, 128.3, 128.3 (C**12**, C**13** and C**14**), 120.9 (Ar-CH), 111.0 (Ar-CH), 50.7 (C**10**), 44.6 (C**4**), 36.3 (C**2**), 24.5 (C**3**); HRMS: $(ESI)^+$ Calculated for $C_{16}H_{16}N_2NaO_2$: 291.1104. Found $[M + Na]^+$: 291.1113. *A ^{1}H NMR spectrum was recorded at 100 °C in DMSO-d_6 and at -50 °C in $CDCl_3$ because at room temperature slow conformational interconversion gave a broad spectrum. The structure of this compound was determined unambiguoulsy by X-ray cystrallography.*



Data for minor product **313b**: m.p.: 115–117 °C (pentane/EtOAc); ν_{max}/ cm^{-1}: 2987 (m), 1685 (s), 1667 (s), 1483 (s), 1406 (s), 1257 (s), 1075 (s), 1066 (s), 1056 (s); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ 7.44 – 7.33 (6H, m, C**9**-H, 2 × C**12**-H, 2 × C**13**-H, C**14**-H), 6.93 (1H, dd, *J* = 4.0, 2.0 Hz, ArC-H), 6.32 (1H, dd, *J* = 4.0, 1.5 Hz, ArC-H), 6.24 (1H, d, *J* = 7.0 Hz, C**4**-H), 5.82 (1H, m, C**3**-H), 4.84 (2H, s, C**10**-H_2), 3.14 (1H, d, *J* = 8.0 Hz, C**2**-H_2); ^{1}H NMR (301 MHz, $CDCl_3$, -50 °C): δ 7.44 – 7.34 (5H, m, 5 × ArC-H), 7.30 (1H, m, ArC-H), 7.10 (1H, dd, *J* = 3.0, 1.5 Hz, ArC-H), 6.33 (dd, *J* = 4.0, 3.0 Hz, ArC-H), 6.12 (1H, dd, *J* = 7.0, 1.0 Hz, C**4**-H), 5.84 (1H, ddd, *J* = 10.0, 7.0, 6.5 Hz, C**3**-H), 5.16 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 4.49 (1H, d, *J* = 14.0 Hz, 1 × C**10**-H_2), 3.22 (1H, dd, *J* = 13.5, 10.0 Hz, 1 × C**2**-H_2), 2.93 (1H, dd, *J* = 13.5, 6.5 Hz,1 × C**2**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.3 (C**1**), 152.6 (C**5**), 135.0 (C**11**), 132.4 (C**6**), 130.0 (Ar-CH), 129.2 (C**4**), 128.9 (2 signals) (C**12**, C**13**), 128.5 (C**14**), 124.9 (C**3**), 120.2 (Ar-CH), 110.9 (Ar-CH), 53.6 (C**10**), 40.3 (C**2**); HRMS: $(ESI)^+$ Calculated for $C_{16}H_{14}N_2NaO_2$: 289.0947. Found $[M + Na]^+$: 289.0951. *A ^{1}H NMR spectrum was recorded at 100 °C in DMSO-d_6 and at -50 °C in $CDCl_3$ because at room temperature slow conformational interconversion gave a broad spectrum.*

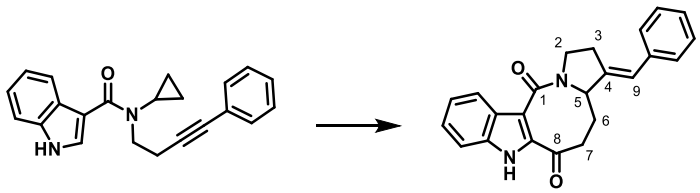
4-phenylbut-3-yn-1-ol



317 319

The title compound was prepared following a modified literature procedure.[210] To an oven dried reaction tube was added CuI (19.0 mg, 0.010 mmol), $PdCl_2(PPh)_3$ (70.2 mg, 0.010 mmol) and Et_3N (8 mL). The tube was fitted with a rubber septum and purged with argon. The resulting solution was stirred at room temperature for 15 minutes then iodobenzene (1.23 mL, 11.0 mmol) and but-3-yn-1-ol (0.76 mL, 10.0 mmol) and another 2 mL of Et_3N were added. The mixture was heated at 65 °C for 12 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound **319** (1.34 g, 85%) as a colourless solid; ν_{max} / cm^{-1}: 3360 (br. s), 30332 (m), 2932 (m), 1675 (s), 1590 (s), 1440 (s), 1042 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.32 (5H, m, 5 × ArC-H), 3.80 (1H, t, *J* = 6.5 Hz, C$\underline{H}_2$), 2.70 (t, *J* = 6.5 Hz, C$\underline{H}_2$). *The spectroscopic properties of this compound were consistent with the data available in literature*.[353]

(*E*)-3-Benzylidene-1,2,3,3a,4,5-hexahydro-6*H*-pyrrolo[1',2':1,8]azocino[4,3-*b*]indole-6,12(7*H*)-dione (310f)



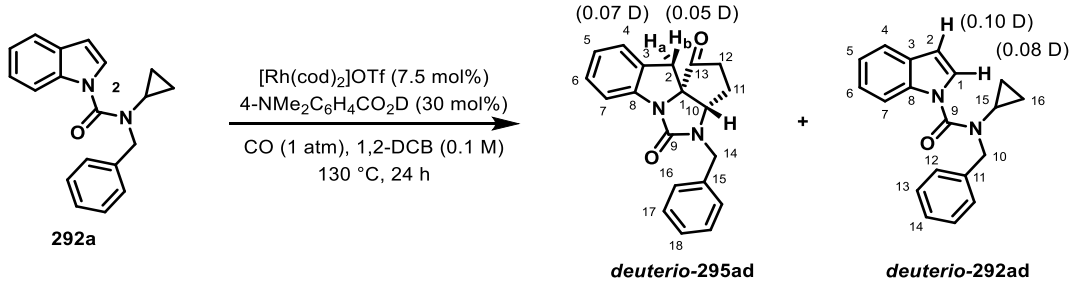
308f **310f**

*Substrate **308f** was synthesised by G.-W. Wang.* An oven dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (3.51 mg, 7.5×10^{-3} mmol, 7.5 mol%), $P(4\text{-}(F)C_6H_4)_3$ (4.74 mg, 0.015 mmol, 15 mol%), 2-nitrobenzoic acid (25.0 mg, 0.10 mmol), and substrate **308a** (32.8 mg, 0.10 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous PhCN (0.1 mL) was added by syringe. The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The reaction mixture was heated at 140 °C for 72 hours. The mixture was cooled to room temperature, concentrated *in vacuo* and the crude residue was purified by flash column chromatography (5–10% acetone/toluene) to yield the title compound **310f** (22.1 mg, 62%) as a yellow solid; m.p. 253–255 °C ($CDCl_3$); ν_{max} / cm^{-1}: 3288 (m), 1657 (s), 1605 (s), 1519 (s), 1456 (s), 1333 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 9.41 (1H, br. s, N$\underline{H}$), 8.05 (1H, d, *J* = 8.0 Hz, 1 × ArC-$\underline{H}$), 7.38 – 7.24 (4H, m, 4 × ArC-$\underline{H}$), 7.18 – 7.14 (4H, m, 4 × ArC-$\underline{H}$), 6.22 (1H, d, *J* = 2.5 Hz, C**9**-$\underline{H}$), 4.60 (1H, dd, *J* = 13.0, 5.0 Hz, C**5**-$\underline{H}$), 4.40 (1H, ddd, *J* = 12.5, 9.0, 5.5 Hz, 1 × C**2**-$\underline{H}_2$), 3.68 (1H, ddd, *J* = 12.5, 9.0, 6.5 Hz, 1 × C**2**-$\underline{H}_2$), 3.20 (1H, ddd, *J* = 13.0, 13.0, 5.5 Hz, 1 × C**7**-$\underline{H}_2$), 3.01 – 2.86 (2H, m, C**3**-$\underline{H}_2$), 3.60 (1H, m, 1 × C**7**-$\underline{H}_2$), 2.22 – 2.01 (2H, m, 2 × C**6**-$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.4 (C**8**), 163.9 (C**1**), 141.0 (C**4**), 136.6 (Ar$\underline{C}$), 136.0 (Ar$\underline{C}$), 133.3 (Ar$\underline{C}$), 128.4 (Ar-$\underline{C}$H), 128.2 (Ar-$\underline{C}$H), 127.7 (Ar-$\underline{C}$H), 127.2 (Ar-$\underline{C}$H), 127.1 (Ar$\underline{C}$), 123.8 (Ar-$\underline{C}$H), 122.8 (C**9**), 122.3 (Ar-

CH), 116.2 (ArC), 111.9 (Ar-CH), 62.7 (C**5**), 44.2 (C**2**), 37.7 (C**7**), 35.9 (C**6**), 27.3 (C**3**); HRMS: (ESI$^+$) Calculated for $C_{23}H_{21}N_2O_2$: 357.1598. Found $[M + H]^+$: 357.1593.

7.5.2 Mechanistic studies from Chapter 4

Eqn 7: Deuterium exchange experiment of the carbonylative cyclisation of indole 292a with 4-N(Me)$_2$C$_6$H$_4$CO$_2$D



p-NMe$_2$C$_6$H$_4$CO$_2$H was initially prepared by repeatedly dissolving *p*-NMe$_2$C$_6$H$_4$CO$_2$H in MeOD-d$_4$ and concentrating the resulting solution *in vacuo*.

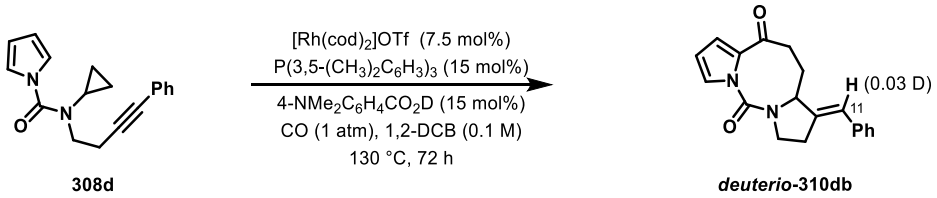
An oven dried reaction tube, fitted with a magnetic stirrer, was charged with [Rh(cod)$_2$]OTf (5.28 mg, 11.2 × 10^{-3} mmol), *p*-NMe$_2$C$_6$H$_4$CO$_2$D (7.47 mg, 45.0 × 10^{-3} mmol), and substrate **292a** (43.5 mg, 0.15 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (1.5 mL) was added by syringe. The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The reaction mixture was heated at 130 °C for 24 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/Hexane then 5% EtOAc/toluene) to afford ***deuterio*-295ad** (25.8 mg, 54%) and ***deuterio*-292ad** (11.7 mg, 27%). The percentage of deuterium incorporation was measured by ^{1}H NMR. Analysis of ***deuterio*-295ad** revealed 7% and 5% deuterium incorporation at the diastereotopic C**2** protons. Analysis of ***deuterio*-292ad** revealed 8% and 10% deuterium incorporation at the C**1** and C**2** protons**.**

Data for ***deuterio*-295ad**: ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.51 (1H, dd, *J* = 8.0, 1.0 Hz, C**7**-H), 7.41 – 7.26 (5H, m, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.24 – 7.17 (2H, m, C**4**-H and C**6**-H), 7.06 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 4.67 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H$_2$), 4.37 (1H, d, *J* = 15.0 Hz, 1 × C**10**-H$_2$), 4.09 (1H, d, *J* = 5.5 Hz, C**15**-H), 3.35 (0.93H, d, *J* = 16.0 Hz, 1 × C**2**-H$_2$), 3.09 (0.95H, d, *J* = 16.0 Hz, 1 × C**2**-H$_2$), 2.62 (1H, ddd, *J* = 17.5, 13.5, 9.0 Hz, 1 × C**12**-H$_2$), 2.38 – 2.19 (2H, m, 1 × C**12**-H$_2$, 1 × C**11**-H$_2$), 1.87 (1H, dddd, *J* = 13.5, 7.5, 5.5, 2.0 Hz, 1 × C**11**-H$_2$).

Data for ***deuterio*-292ad**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, m, C**7**-H), 7.49 (1H, dd, *J* = 7.5, 1.0 Hz, C**4**-H), 7.34 (0.92H, d, *J* = 3.5 Hz, C**1**-H), 7.31 – 7.15 (6H, m, C**6**-H , 2 × C**12**-H, 2 × C**13**-H and

C**14**-H), 7.11 (1H, dd, *J* = 7.5, 1.0 Hz, C**5**-H), 6.49 (0.90H, d, *J* = 3.5 Hz, C**2**-H), 4.61 (2H, s, C**10**-H_2), 2.54 (1H, tt, *J* = 7.0, 4.0 Hz, C**15**-H), 0.62 – 0.45 (4H, m, 2 × C**16**-H_2).

Eqn 11: Deuterium exchange experiment of the carbonylative cyclisation of pyrrole 308d with 4-N(Me)$_2$C$_6$H$_4$CO$_2$D

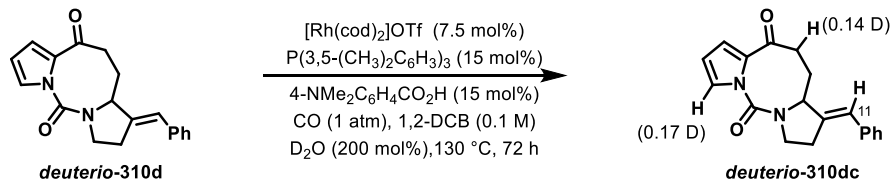


308d ***deuterio*-310db**

An oven dried reaction tube, fitted with a magnetic stirrer, was charged with [Rh(cod)$_2$]OTf (3.52 mg, 7.0 μmol, 7.5 mol%), 4-NMe$_2$C$_6$H$_4$CO$_2$D (2.30 mg, 14.0 μmol, 15 mol%), tris(3,5-dimethylphenyl)phosphine (4.83 mg, 14.0 μmol, 15 mol%) and *N*-cyclopropyl-*N*-(4-phenylbut-3-yn-1-yl)-1*H*-pyrrole-1-carboxamide **308d** (25.8 mg, 0.093 mmol). The tube was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (0.93 mL) was added by syringe. The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. The reaction mixture was heated at 130 °C for 72 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified by column chromatography (5% EtOAc/toluene) to yield the title compound ***deuterio*-310db** (19.7 mg, 70%) as a colourless oil. The percentage of deuterium incorporation was measured by ^{1}H NMR. Analysis of ***deuterio*-310d** revealed 3% deuterium incorporation at the C**11** proton.

Data for product ***deuterio*-310db**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49 (1H, dd, *J* = 3.0, 2.0 Hz, ArC-H), 7.39 – 7.21 (5H, m, 5 × ArC-H), 7.10 (1H, dd, *J* = 4.0, 2.0 Hz, ArC-H), 6.49 (0.97H, d, *J* = 2.5 Hz, C**11**-H), 6.36 (1H, dd, *J* = 4.0, 3.0 Hz, ArC-H), 4.49 (1H, dd, *J* = 11.5, 6.0 Hz), 4.12 (1H, ddd, *J* = 12.0, 9.5, 5.0 Hz), 3.75 (1H, ddd, *J* = 12.0, 9.4, 6.5 Hz), 3.05 (1H, m,), 2.93 – 2.84 (2H, m), 2.10 – 1.94 (2H, m).

Eqn 12: Deuterium exchange experiment of the carbonylative cyclisation of pyrrole 308d with D$_2$O



***deuterio*-310d** ***deuterio*-310dc**

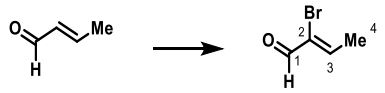
An oven dried reaction tube, fitted with a magnetic stirrer, was charged with [Rh(cod)$_2$]OTf (2.48 mg, 5.2 μmol, 7.5 mol%), 4-(dimethylamino)benzoic acid (1.77 mg, 10.5 μmol, 15 mol%), tris(3,5-dimethylphenyl)phosphine (3.68 mg, 10.5 μmol, 15 mol%) and **310d** (21.6 mg, 0.071 mmol). The tube

was fitted with a rubber septum and purged with argon. Anhydrous 1,2-DCB (0.71 mL) was added by syringe. The reaction vessel was purged with CO for 10 minutes and the solution was subsequently sparged with CO for approximately 20 seconds. Then the CO balloon was removed and D_2O (2.5 uL, 0.14 mmol) was added. The tube was sealed and the reaction was heated at 130 °C for 72 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude mixture was purified by column chromatography (5% EtOAc/toluene) to yield the title compound ***deuterio*-310dc** (17.9 mg, 82%) as a colourless oil. The percentage of deuterium incorporation was measured by ^{1}H NMR. Analysis of ***deuterio*-310dc** revealed no exchange at the vinylic position of the product was observed.

Data for product ***deuterio*-310db**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (0.83H, dd, *J* = 3.0, 2.0 Hz, ArC-H), 7.41 – 7.20 (5H, m, 5 × ArC-H), 7.10 (1H, m, ArC-H), 6.49 (1H, d, *J* = 2.5 Hz, C**11**-H), 6.37 (1H, dd, *J* = 4.0, 3.0 Hz, ArC-H), 4.49 (1H, dd, *J* = 11.5, 6.0 Hz), 4.13 (1H, ddd, *J* = 12.0, 9.5, 5.0 Hz), 3.75 (1H, ddd, *J* = 12.0, 9.5, 6.5 Hz), 3.07 (1H, m), 2.93 – 2.84 (0.86H, m), 2.10 – 1.94 (2H, m).

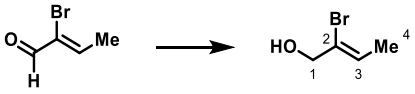
7.5 Experimental procedures for the studies in Chapter 5

(*Z*)-2-Bromobut-2-enal



To a solution of *trans*-crotonaldehyde (2.95 mL, 35.7 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added bromine (1.85 mL, 36.1 mmol) in CH_2Cl_2 (5 mL) dropwise over 10 minutes *via* a dropping funnel. The reaction mixture was stirred at 0 °C for 1 hour. Triethylamine (6.00 mL, 43.2 mmol) was added, the reaction mixture was warmed to room temperature and stirred for an additional 1.5 hours. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The organic layer was washed with 1 M aq. HCl (10 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound (4.68 g, 89%, >95:5 *Z*:*E*) as a pale yellow oil. The product was used in the following step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (1H, d, *J* = 1.0 Hz, C**1**-H), 7.27 (1H, q, *J* = 6.5 Hz, C**3**-H), 2.14 (3H, dd, *J* = 6.5, 1.0 Hz, C**4**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 186.2 (C**1**), 151.3 (C**3**), 130.2 (C**2**), 18.1 (C**4**). *The spectroscopic properties of this compound were consistent with the data available in literature*.[251]

(*Z*)-2-Bromobut-2-en-1-ol (371)

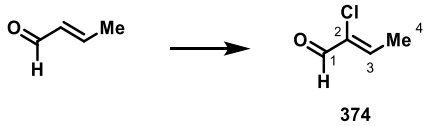


371

To a solution of **(***Z*)-2-Bromobut-2-enal (4.72 g, 31.7 mmol) in THF/H_2O (9:1, 80 mL) at 0 °C was added $NaBH_4$ (740 mg, 19.0 mmol) portion wise over 10 minutes. The reaction mixture was stirred for

1 hour and then quenched with 1 M aq. HCl (10 mL) and warmed to room temperature. The reaction mixture was diluted with EtOAc/hexane (1:4, 80 mL) and H_2O (100 mL). The aqueous layer was separated and extracted with EtOAc/hexane (1:4, 80 mL). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound **371** (4.08 g, 86%) as a pale yellow oil. The product was used in the following step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (1H, qt, *J* = 6.5, 1.0 Hz, C**3**-H), 4.25 (2H, qd, *J* = 1.0, 1.0 Hz, C**1**-H_2), 1.78 (3H, dt, *J* = 6.5, 1.0 Hz, C**4**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 128.0 (C**3**), 125.4 (C**2**), 68.7 (C**1**), 16.5 (C**4**).*The spectroscopic properties of this compound were consistent with the data available in literature*.[251]

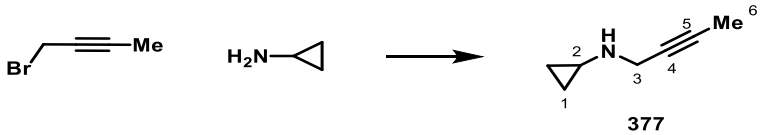
(*Z*)-2-Chlorobut-2-enal (374)



374

*The title compound **374** was prepared following a literature procedure.*[254] To a solution of *trans*-crotonaldehyde (1.05 g, 15.0 mmol) in CH_2Cl_2 (50 mL) was added (diacetoxyiodo)benzene (5.79 g, 18.6 mmol) and pyridine hydrochloride (5.18 g, 45.0 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was transferred to a separating funnel and washed with 1 M aq. HCl (20 mL). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% Et2O/petrol) to give the title compound **374** (1.14 g, 73%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (1H, s, C**1**-H), 6.97 (1H, q, *J* = 7.0 Hz, C**3**-H), 2.13 (3H, d, *J* = 7.0 Hz, C4-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.7 (C**1**), 147.1 (C**3**), 136.9 (C**2**), 15.4 (C4). *The spectroscopic properties of this compound were consistent with the data available in literature*.[354]

***N*-(But-2-yn-1-yl)cyclopropanamine (377)**

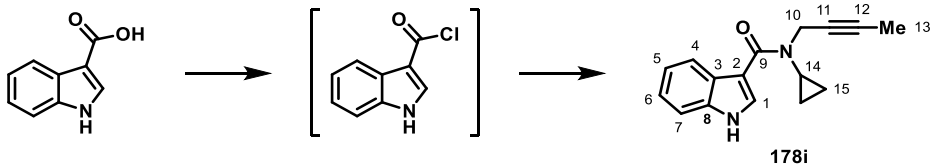


377

To a solution of 1-bromobut-2-yne (0.86 mL, 10.0 mmol) in MeCN (30 mL) was added a solution of cyclopropylamine (4.46 mL, 50.0 mmol) in MeCN (5mL) over 10 minutes at room temperature. After addition was complete, the reaction mixture was stirred for a further 3 hours at room temperature, diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2 × 20 mL). The organic layer was separated and washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound **377**

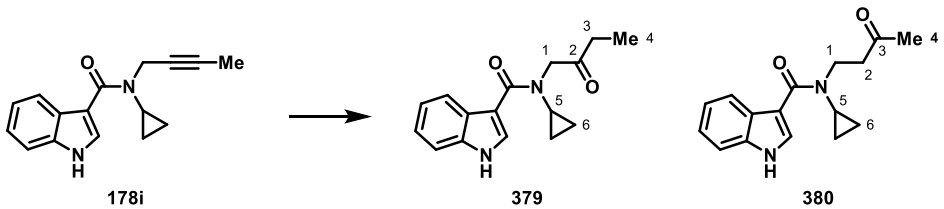
(750 mg, 69%) as a colourless oil; ν_{max}/ cm^{-1}: 3749 (br. m), 2926 (m), 1441 (s), 1321 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (2H, q, *J* = 2.5 Hz, C**3**-$\underline{H}_2$), 2.30 (1H, m, C**2**-$\underline{H}$), 1.81 (3H, t, *J* = 2.5 Hz, C**6**-$\underline{H}_3$), 1.75 (1H, br. s, N$\underline{H}$), 0.48 – 0.33 (4H, m, 2 × C**1**-$\underline{H}_2$);^{13}C NMR (101 MHz, $CDCl_3$): δ 78.7, 77.7 (C**4** and C**5**), 38.5 (C**3**), 29.7 (C**2**), 6.3 (C**1**), 3.6 (C**6**); LRMS: (ESI)$^+$ Calculated for $C_7H_{12}N$: 109.09. Found [M + H] $^+$: 109.09.

***N*-(But-2-yn-1-yl)-*N*-cyclopropyl-1*H*-indole-3-carboxamide (178i)**



To a solution of 1H-indole-3-carboxylic acid (500 mg, 3.10 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.26 mL, 3.10 mmol) dropwise over five minutes and DMF (2 drops) at 0 °C. After addition was complete, the mixture was warmed to room temperature and stirred for a further 2 hours. The reaction mixture was concentrated *in vacuo* and then suspended in CH_2Cl_2 (15 mL). A solution of *N*-(but-2-yn-1-yl)cyclopropanamine **377** (338 mg, 3.10 mol) in 5 mL of CH_2Cl_2 was added and triethylamine (0.65 mL, 4.65 mmol). The reaction mixture was stirred at room temperature for 16 hours, diluted with CH_2Cl_2 (25 mL) and washed with H_2O (3 × 20 mL). The organic layer was separated and washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was recrystallised from MeOH to give the title compound **178i** (513 mg, 66%) as a white crystalline solid; m.p.: 159–160 °C (MeOH); ν_{max}/ cm^{-1}: 3158 (m), 2916 (m), 1586 (s), 1522 (s), 1439 (s), 1312 (s), 1219 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (1H, br. s, N$\underline{H}$), 8.03 (1H, dd, *J* = 6.5, 3.0 Hz, C**4**-$\underline{H}$), 7.33 (1H, d, *J* = 3.0 Hz, C**1**-$\underline{H}$), 7.25 (1H, m, C**7**-$\underline{H}$), 7.19 – 7.12 (2H, m, C**5**-$\underline{H}$ and C**6**-$\underline{H}$), 4.30 (2H, q, *J* = 2.5 Hz, C**10**-$\underline{H}_2$), 2.89 (1H, m, C**14**-$\underline{H}$), 1.81 (3H, t, *J* = 2.5 Hz, C**13**-$\underline{H}_3$), 0.71 (4H, m, 2 × C**15**-$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8 (C**9**), 135.7 (C**8**), 128.4 (C**1**), 127.0 (C**3**), 122.6 (C**6**), 121.3, 121.1 (C**4** and C**5**), 111.7 (C**7**), 110.9 (C**2**), 79.0, 75.7 (C**11** and C**12**), 38.5 (C**10**), 31.1 (C**14**), 9.7 (C**15**), 3.8 (C**13**); HRMS: (ESI)$^+$ Calculated for $C_{16}H_{16}N_2O$: 253.1335. Found [M + H] $^+$: 253.1336.

***N*-Cyclopropyl-*N*-(2-oxobutyl)-1*H*-indole-3-carboxamide (379)** and ***N*-Cyclopropyl-*N*-(3-oxobutyl)-1*H*-indole-3-carboxamide (380)**



General Procedure C: Indole **178i** (37.8 mg, 0.15 mmol) was employed and the reaction mixture was heated at 140 °C for 72 h. The reaction was cooled to room temperature and concentrated *in vacuo*. *An*

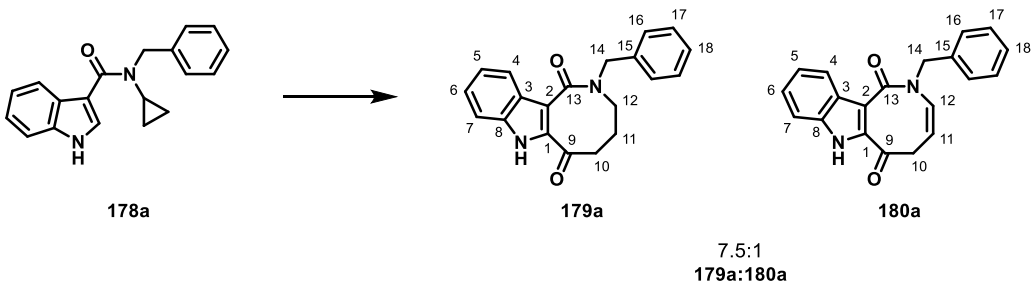
*in situ yield was obtained by ^{1}H NMR spectroscopy using 1,4-dinitrobenzene as an internal standard; a 25% yield of **379** and 9% yield of **380** were observed. The products could not be readily separated from the ligand, starting material and the other side products, the structure of the products **379** and **380** were determined by analysis of the ^{1}H NMR spectrum of the reaction mixture and corroborated by COSY data.*

Data for **379**: *Characteristic signals only:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.40 (2H, s, C**1**-$\underline{H}_2$), 3.13 – 2.55 (2H, q, *J* = 7.5 Hz, C**3**-$\underline{H}_2$), 1.12 (3H, t, *J* = 7.5 Hz, C**4**-$\underline{H}_3$).

Data for **380**: *Characteristic signals only:* ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46 (2H, t, *J* = 6.0 Hz, C**1**-$\underline{H}_2$), 2.99 (2H, t, *J* = 6.0 Hz, C**2**-$\underline{H}_2$), 2.12 (3H, s, C**4**-$\underline{H}_3$).

Data for both **379** and **380**: HRMS: $(ESI)^+$ Calculated for $C_{16}H_{19}N_2O_2$: 271.1434. Found $[M + H]^+$: 271.1441.

2-Benzyl-2,3,4,5-tetrahydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (179a) and **(*Z*)-2-Benzyl-2,5-dihydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (180a)**



*Procedure for the Rh(I)-catalysed carbonylative cyclisation of indole **178a** in a ChemSCAN II® reactor.* To a stainless stain ChemSCAN II® reactor vessel was added indole **178a** (290 mg, 1.00 mmol), 2-nitrobenzoic acid (250 mg, 1.50 mmol), $P(4\text{-}(F)C_6H_4)_3$ (47.4 mg, 0.150 mmol) and $[Rh(cod)OMe]_2$ (18.0 mg, 0.038 mmol). The reagents were dissolved in anhydrous PhCN (3.0 mL). The reaction vessel was attached to a ChemSCANII® reactor and purged with nitrogen (× 4 cycles) and then purged with CO (×4 cycles). The vessel was heated at 130 °C at 3 bar of CO for 24 hours. After this time, the reaction vessel was cooled to room temperature, vented and purged with nitrogen. The reaction mixture was transferred to a round-bottom flask, washing with MeOH (~2 mL) and concentrated in *vacuo*. The crude material was purified by flash column chromatography (80 g silica column, 20–70% EtOAc/hexane, 16 column volumes) to give the title compound **179a** (146 mg, 45%) as an off-white solid and the title compound **180a** (19.9 mg, 6%) as an off-white solid. *The spectroscopic properties of **179a** and **180a** were consistent with the data previously reported in this thesis*.

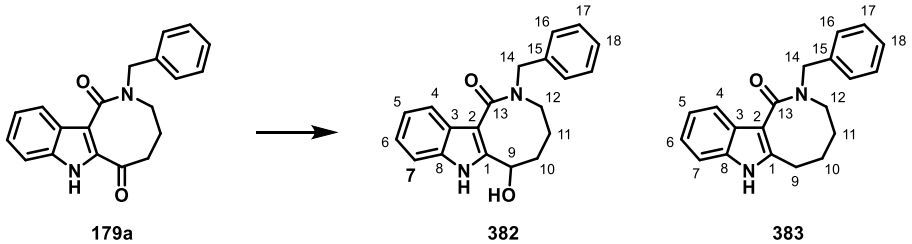
Data for major compound **179a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (1H, br. s, N$\underline{H}$), 8.12 (1H, d, *J* = 8.0 Hz, C**4**-$\underline{H}$), 7.48 – 7.21 (8H, m, C**5**-$\underline{H}$, C**6**-$\underline{H}$, C**7**-$\underline{H}$, 2 × C**16**-$\underline{H}$, 2 × C**17**-$\underline{H}$ and C**18**-$\underline{H}$), 5.31 (1H, m, 1 × C**14**-$\underline{H}_2$), 4.53 (1H, d, *J* = 14.5 Hz, 1 × C**14**-$\underline{H}_2$), 3.82 (1H, m, 1 × C**12**-$\underline{H}_2$), 3.32 (1H, m, 1 ×

C**12**-H$_2$), 3.14 (1H, m, 1 × C**10**-H$_2$), 2.63 (1H, d, *J* = 12.5 Hz, 1 × C**10**-H$_2$), 2.07 (1H, d, *J* = 12.0 Hz, 1 × C**11**-H$_2$), 1.84 (1H, m, 1 × C**11**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.1 (C**9**), 166.3 (C**13**), 137.5 (C**15**), 136.2 (C**8**), 133.5 (C**1**), 128.9, 128.4, 128.3 (C**3**, C**16** and C**17**), 127.9 (C**6**), 127.4 (C**18**), 123.8 (C**4**), 122.4 (C**5**), 115.2 (C**2**), 112.1 (C**7**), 48.6 (C**14**), 45.8 (C**12**), 36.9 (C**10**), 26.5 (C**11**).

Data for minor compound **180a**: m.p.: 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (1H, br. s, NH), 8.05 (1H, d, *J* = 8.0, Hz, C**4**-H), 7.51 – 7.23 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 6.16 (1H, dd, *J* = 7.5, 1.0 Hz, C**12**-H), 5.64 (1H, ddd, *J* = 10.0, 7.5, 7.0 Hz, C**11**-H), 5.30 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 4.77 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 3.53 (1H, ddd, *J* = 12.5, 10.0, 1.0 Hz, 1 × C**10**-H$_2$), 3.11 (1H, dd, *J* = 12.5, 7.0 Hz, 1 × C**10**-H$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.0 (C**9**), 163.9 (C**13**), 136.8 (C**15**), 135.6 (C**8**), 131.9 (C**12**), 130.6 (C**1**), 128.7, 128.5, 128.4 (C**3**, C**16** and C**17**), 127.8 (C**18**), 126.9 (C**6**), 123.7 (C**4**), 122.3 (C**5**), 120.4 (C**11**), 114.6 (C**2**), 111.8 (C**7**), 51.2 (C**14**), 40.1 (C**10**).

Figure 6:[355] A) Image of a ChemScan II® reactor vessel and stirrer motor. B) Image of the ChemSCAN II®. A ChemSCAN II® consists of 8 reactor vessels that are independently controlled and monitored.

2-Benzyl-6-hydroxy-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-1-one (382) and **2-Benzyl-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-1-one (383)**



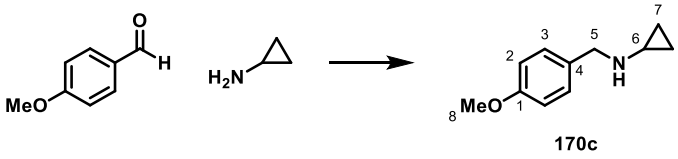
Indole **179a** (48.0 mg, 0.151 mmol) was dissolved in ethanol (2 mL) ethyl acetate (1 mL). The reaction mixture was hydrogenated using the H-cube (settings: 60 °C, 10 bar, 1mL/min flow rate) and 20% Pd(OH)$_2$/C CatCart 30 as the catalyst. The crude material was concentrated *in vacuo*, dissolved in DMSO (1.2 mL) and purified by preparative high-performance liquid chromatography using an XSelect CSH C18 column (100 mm x 30 mm, 5 µm). The preprative HPLC was conducted using a 40 mL/min flow rate using a gradient elution (30–100%, **A**:**B**, with the eluents as **A**) 10 mM ammonium bicarbonate

in water adjusted to pH 10 with ammonia solution and **B**) acetonitrile) over 27.0 minutes. The fractions containing the products were concentrated under reduced pressure to give the title compounds **382** (10.5 mg, 21%) as an off-white solid and **383** (9.1 mg, 20%) as an off-white solid.

Data for compound **382**: m.p: 180–182 °C (MeOH); ν_{max}/ cm^{-1}: 3264 (br. s), 3158 (br. s), 2974 (m), 2862 (m), 1590 (s), 1484 (s), 1454 (s), 1267 (s), 1189 (s), 1065 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (1H, br. s, NH), 7.66 (1H, dd, *J* = 8.0, 1.5 Hz, C**4**-H), 7.40 – 7.30 (5H, m, C**7**-H, 2 × C**16**-H, 2 × C**17**-H), 7.26 (1H, m, C**18**-H), 7.09 (1H, ddd, *J* = 8.0, 7.0, 1.5 Hz, C**6**-H), 7.02 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-H), 5.61 (1H, d, *J* = 6.0 Hz, OH), 4.86 (1H, br. m, C**9**-H), 4.69 (2H, br. m, C**14**-H_2), 3.36 – 3.16 (2H, br. m, C**12**-H_2), 2.03 – 1.76 (3H, m, 1 × C**10**-H_2 and C**11**-H_2), 1.67 (1H, m, 1 × C**10**-H_2); ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.9 (C**13**), 141.9 (C**1**), 138.6 (C**15**), 135.4 (C**8**), 128.6 (C**17**), 128.0 (C**16**), 127.8 (C**3**), 127.2 (C**18**), 121.9 (C**6**), 120.5 (C**4**), 119.7 (C**5**), 111.3 (C**7**), 105.3 (C**2**), 66.1 (C**9**), 47.5 (C**14**), 45.8 (C**12**), 29.7 (C**10**), 22.9 (C**11**); HRMS: $(ESI)^+$ Calculated for $C_{20}H_{20}N_2NaO_2$: 343.1417. Found $[M + Na]^+$: 343.1418.

Data for compound **383**: m.p.: 159–162 °C (CH_2Cl_2); ν_{max}/ cm^{-1}: 3323 (br. s), 1556 (s), 1482 (m), 1365 (m), 1200 (s), 1046 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (1H, s, NH), 8.00 – 7.92 (1H, m, C**4**-H), 7.45 – 7.08 (8H, m, C**5**-H, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 4.83 (2H, s, C**14**-H_2), 3.47 (2H, br. m, C**9**-H_2), 2.90 (2H, br. m, C**12**-H_2), 1.91 (2H, br. m, C**11**-H_2), 1.71 (2H, br. m, C**10**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (C**13**), 139.1 (C**1**), 138.1 (C**15**), 135.4 (C**8**), 128.9 (C**3**), 128.7, 128.3, 127.4 (C**16**, C**17** and C**18**), 122.5 (C**6**), 121.1, 120.8 (C**4** and C**5**), 110.1 (C**7**), 107.8 (C**2**), 48.3 (C**14**), 46.0 (C**12**), 28.1 (C**9**), 27.6 (C**11**), 20.8 (C**10**); LRMS: $(ESI)^+$ Calculated for $C_{20}H_{20}NO$: 305.10. Found $[M + H]^+$: 305.10.

***N*-(4-Methoxybenzyl)cyclopropanamine (170c)**

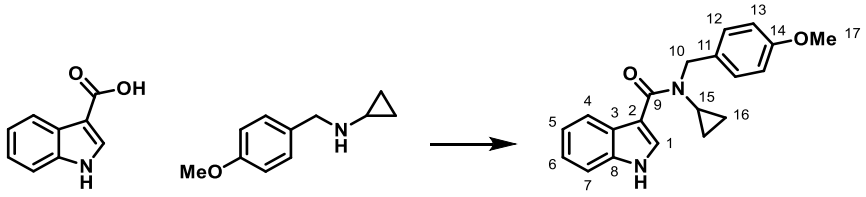


170c

A solution of *p*-anisaldehyde (4.87 mL, 40.0 mmol), cyclopropylamine (3.33 mL, 48.0 mmol) and $NaHCO_3$ (5.04 g, 60 mmol) in MeOH (70 mL) were refluxed for 16 hours. The resulting suspension was cooled to 0 °C and $NaBH_4$ (1.89 g, 50.0 mmol) was added portion wise over 10 minutes. The reaction was warmed to room temperature and stirred for an additional 3 hours. The reaction mixture was concentrated *in vacuo* before the addition of saturated aqueous $NaHCO_3$ (100 mL). The solution was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound **170c** (6.93 g, 98%) as a pale yellow oil. The crude material was used without further purification. ν_{max}/ cm^{-1}: 3320 (m), 2995 (m), 1611 (m), 1510 (s), 1242 (s), 1173 (s), 1034 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.21 (2H,

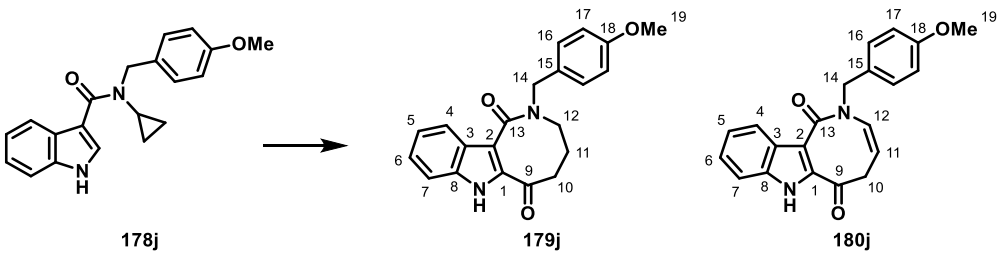
m, 2 × C**3**-H), 6.89 – 6.81 (2H, m, 2 × C**2**-H), 3.80 (3H, s, C**8**-H$_3$), 3.78 (2H, s, C**5**-H$_2$), 2.14 (1H, m, C**6**-H), 1.71 (1H, br. s, NH), 0.47 – 0.30 (4H, m, 2 × C**7**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7 (C**1**), 132.9 (C**4**), 129.5 (C**3**), 113.9 (C**2**), 55.4 (C**8**), 53.2 (C**5**), 30.1 (C**6**), 6.5 (C**7**). *The spectroscopic properties of this compound were consistent with the data available in literature*.[118]

-cyclopropyl-*N*-(4-methoxybenzyl)-1*H*-indole-3-carboxamide (178j)



General Procedure A: 1*H*-Indole-3-carboxylic acid (2.01 g, 12.5 mmol) and *N*-(4-methoxybenzyl)cyclopropanamine **170c** (2.32 g, 13.1 mmol) were employed and the reaction was stirred at r.t. for 12 hours. The crude residue was recrystallised from MeOH to give the title compound **178j** (2.46 mg, 62%) as white crystalline solid; m.p.: 149–151 °C (MeOH); ν_{max}/ cm^{-1}: 3300 (m), 3007 (m), 1509 (s), 1439 (s), 1244 (s), 1231 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (1H, s, NH), 7.97 (1H, m, C**4**-H), 7.27 – 7.22 (2H, m, 2 × C**12**-H), 7.19 – 7.08 (4H, m, C**1**-H, C**5**-H, C**6**-H and C**7**-H), 6.89 – 6.82 (2H, m, 2 × C**13**-H), 4.75 (2H, s, C**10**-H$_2$), 3.78 (3H, s, C**17**-H$_3$), 2.59 (1H, m, C**15**-H), 0.63 – 0.59 (4H, m, 2 × C**16**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2 (C**9**), 158.9 (C**14**), 135.8 (ArC), 130.6 (C**11**), 129.2 (C**12**), 128.0 (C**1**), 126.9 (ArC), 122.6, 121.2, 121.1 (C**4**, C**5** and C**6**), 114.1 (C**13**), 111.8 (C**7**), 111.4 (C**2**), 55.4 (C**17**), 51.1 (C**10**), 30.7 (C**15**), 10.2 (C**16**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{21}N_2O_2$: 321.1597. Found [M + H]$^+$: 321.1591.

2-(4-Methoxybenzyl)-2,3,4,5-tetrahydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (179j) and **(*Z*)-2-(4-Methoxybenzyl)-2,5-dihydro-1*H*-azocino[4,3-*b*]indole-1,6(7*H*)-dione (180j)**

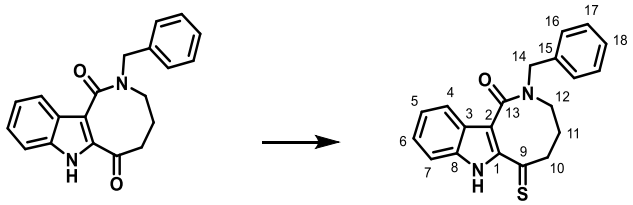


General Procedure C: Indole **178j** (49.8 mg, 0.150 mmol) was employed and the reaction mixture was heated at 130 °C for 72 h. The residue was purified by flash column chromatography (50% EtOAc/hexane) to yield the title compound **179j** (27.6 mg, 51%) as a yellow solid. Analysis of the crude reaction mixture by ^{1}H NMR revealed a 10:1 (**179j**:**180j**) mixture of products. The minor product **180j** was not isolated.

Data for major compound **179j**: m.p.: 151–153 °C (MeOH); ν_{max}/ cm^{-1}: 3132 (br. s), 2925 (m), 1653 (s), 1600 (s), 1513 (s), 1240 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (1H, s, NH), 8.14 (1H, dd, *J* = 8.5, 1.0 Hz, C**4**-H), 7.47 – 7.40 (2H, m, C**6**-H and C**7**-H), 7.42 – 7.35 (2H, m, 2 × C**16**-H), 7.28 (1H, m, C**5**-H), 6.97 – 6.81 (2H, m, 2 × C**17**-H), 5.20 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 4.55 (d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 3.92 – 3.71 (4H, m, 1 × C**12**-H$_2$ and C**19**-H$_3$), 3.33 (1H, d, *J* = 14.5 Hz, 1 × C**12**-H$_2$), 3.12 (1H, m, 1 × C**10**-H$_2$), 2.64 (1H, m, 1 × C**10**-H$_2$), 2.03 (1H, m, 1 × C**11**-H$_2$), 1.85 (1H, m, 1 × C**11**-H$_2$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.0 (C**9**), 166.0 (C**13**), 159.2 (C**18**), 136.0 (C**8**), 133.4 (C**1**), 129.7 (C**15**), 129.6 (C**16**), 128.1 (C**3**), 127.2 (C**6**), 123.8 (C**4**), 122.3 (C**5**), 115.2 (C**2**), 114.2 (C**17**), 111.9 (C**7**), 55.3 (C**19**), 48.0 (C**14**), 45.6 (C**12**), 36.8 (C**10**), 26.4 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{21}H_{21}N_2O_3$: 349.1547. Found [M + H] $^+$: 349.1522.

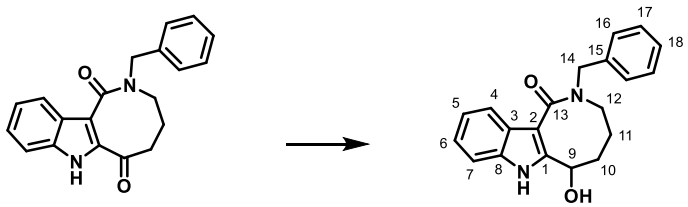
Data for minor compound **180j**: *Characteristic signals only*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (1H, d, *J* = 7.5 Hz, C**12**-H), 5.62 (1H, ddd, *J* = 10.0, 7.5, 7.0 Hz, C**11**-H).

2-Benzyl-6-thioxo-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-1-one (389)



To a solution of substrate **179a** (40.0 mg, 0.126 mmol) in THF (1.3 mL) was added Lawessons's reagent (50.8 mg, 0.126 mmol). The reaction mixture was heated at reflux for 6 hours and then cooled to room temperature. The reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL), H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5% acetone/toluene) to afford the title compound **389** (27.8 mg, 66%) as a yellow oil. ν_{max}/ cm^{-1}: 3224 (br. s), 3061 (m), 2922 (m), 1607 (s), 1505 (s), 1496 (s), 1333 (s), 1210 (s), 1130 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.4 (1H, br. s, NH), 8.08 (d, *J* = 8.5 Hz, C**4**-H), 7.46 – 7.25 (7H, m, C**6**-H, C**7**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 7.22 (1H, m, C**5**-H), 5.38 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 4.43 (1H, d, *J* = 14.5 Hz, 1 × C**14**-H$_2$), 3.74 (1H, ddd, *J* = 15.0, 4.0, 4.0 Hz, 1 × C**12**-H$_2$), 3.61 (1H, ddd, *J* = 13.0, 4.0, 4.0 Hz, 1 × C**10**-H$_2$), 3.37 (1H, dd, *J* = 13.0, 4.0 Hz, 1 × C**10**-H$_2$), 3.24 (1H, dd, *J* = 15.0, 5.0 Hz, 1 × C**12**-H$_2$), 2.12 (1H, m, 1 × C**11**-H$_2$), 1.87 (1H, m, 1 × C**11**-H$_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 224.8 (C**9**), 166.5 (C**13**), 140.2 (C**1**), 138.8 (C**8**), 137.5 (C**15**), 129.4 (C**3**), 128.9 (C**16**), 128.4, 128.3 (C**6** and C**17**), (C18), 127.9 (C**18**), 124.8 (C**4**), 122.8 (C**5**), 112.4 (C**2**), 111.9 (C**7**), 48.5 (C**14**), 45.9 (C**10**), 45.4 (C**12**), 30.3 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{20}H_{18}N_2NaOS$: 357.1032. Found [M + Na] $^+$: 357.1048.

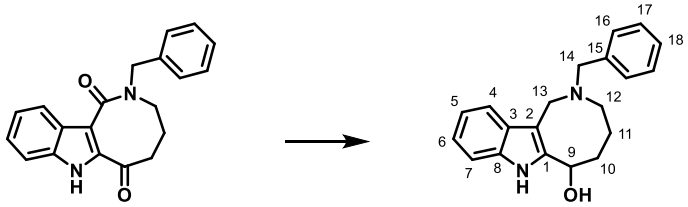
2-Benzyl-6-hydroxy-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-1-one (382)



179a **382**

To a solution of indole **179a** (31.9 mg, 0.10 mmol) in THF (1.0 mL) at 0 °C was added $LiAlH_4$ (0.10 mL, 0.10 mmol, 1.0 M in THF) dropwise over 10 minutes. After addition was complete, stirring was maintained for a further 30 minutes, after which time the reaction was heated at reflux for 16 hours. The mixture was cooled to 0 °C and H_2O (0.5 mL) was added, followed by 15% aqueous NaOH solution (0.5 mL) and a further portion of H_2O (1 mL). The resulting suspension was stirred for 30 minutes and warmed to room temperature. EtOAc (5 mL) and Na_2SO_4 were added and the suspension was filtered through celite®, washing with EtOAc (10 mL). The solution was concentrated *in vacuo* to afford the title compound **382** (24.0 mg, 75 %) as a colourless solid. The product was obtained with good purity and not purified further. *The spectroscopic properties of this compound were consistent with the data previously reported in this thesis*. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (1H, br. s, NH), 7.66 (1H, dd, *J* = 8.0, 1.5 Hz, C**4**-H), 7.40 – 7.30 (5H, m, C**7**-H, 2 × C**16**-H, 2 × C**17**-H), 7.26 (1H, m, C**18**-H), 7.09 (1H, ddd, *J* = 8.0, 7.0, 1.5 Hz, C**6**-H), 7.02 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-H), 5.61 (1H, d, *J* = 6.0 Hz, OH), 4.86 (1H, br. m, C**9**-H), 4.69 (2H, br. m, C**14**-H_2), 3.36 – 3.16 (2H, br. m, C**12**-H_2), 2.03 – 1.76 (3H, m, 1 × C**10**-H_2 and C**11**-H_2), 1.67 (1H, m, 1 × C**10**-H_2); ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.9 (C**13**), 141.9 (C**1**), 138.6 (C**15**), 135.4 (C**8**), 128.6 (C**17**), 128.0 (C**16**), 127.8 (C**3**), 127.2 (C**18**), 121.9 (C**6**), 120.5 (C**4**), 119.7 (C**5**), 111.3 (C**7**), 105.3 (C**2**), 66.1 (C**9**), 47.5 (C**14**), 45.8 (C**12**), 29.7 (C**10**), 22.9 (C**11**).

2-Benzyl-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-6-ol (390)

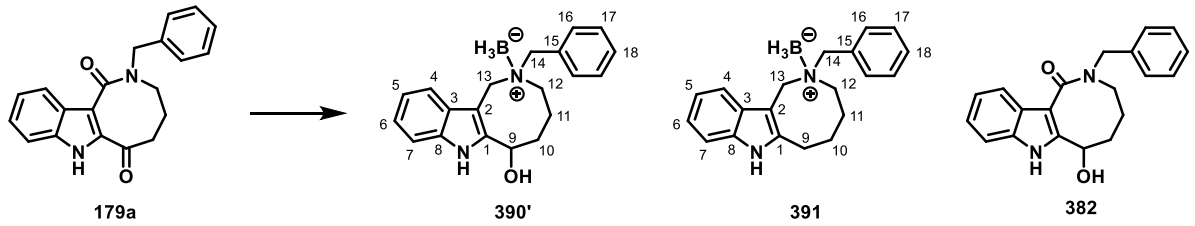


179a **390**

This procedure was carried out in 3 identical reaction tubes in parallel. To a flame-dried screw-top tube, fitted with a rubber septum under an atmosphere of nitrogen was added indole **179a** (111 mg, 0.356 mmol) and THF (4.0 mL). The reaction tube was placed in an ice bath before the dropwise addition of $LiAlH_4$ (1.05 mL, 1.05 mmol, 1.0 M in THF) dropwise over 10 minutes. After addition was complete, stirring was maintained for a further 30 minutes, after which time the reaction tube was sealed

and heated at 80 °C for 16 hours. *Caution: Use a blast shield.* The reaction mixture was cooled to 0 °C, diluted with Et_2O (5 mL) and quenched by careful addition of H_2O (0.2 mL), followed by 15% aqueous NaOH solution (0.2 mL). An additional 1 mL of H_2O was added and the resulting suspension was stirred for 20 minutes and then warmed to room temperature. *At this point, the 3 identical reaction tubes were combined* and filtered through celite®, washing with EtOAc (20 mL). The filtrate was transferred to a separating funnel with H_2O (10 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (0–5% MeOH/CH_2Cl_2) to give the title compound **390** (305 mg, 93%) as a colourless solid; m.p.: 164–167 °C (MeOH); ν_{max}/ cm^{-1}: 3191 (br. s), 2920 (m), 1453 (s), 1338 (s), 1234 (s), 1205 (s), 1062 (s), 1010 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (1H, br. s, N<u>H</u>), 7.38 – 7.23 (7H, m, C**4**-<u>H</u>, C**7**-<u>H</u>, 2 × C**16**-<u>H</u>, 2 × C**17**-<u>H</u> and C**18**-<u>H</u>), 7.12 (1H, ddd, *J* = 8.0, 7.0, 1.5 Hz, C**6**-<u>H</u>), 7.06 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-<u>H</u>), 4.89 (1H, dd, *J* = 4.5, 3.0 Hz, C**9**-<u>H</u>), 4.15 (1H, d, *J* = 16.0 Hz, 1 × C**13**-<u>H_2</u>), 3.90 (1H, d, *J* = 13.0 Hz, 1 × C**14**-<u>H_2</u>), 3.78 (1H, d, *J* = 13.0 Hz, 1 × C**14**-<u>H_2</u>), 3.69 (1H, d, *J* = 16.0 Hz, 1 × C**13**-<u>H_2</u>), 2.91 (1H, ddd, *J* = 12.0, 4.0, 1.0 Hz, 1 × C**12**-<u>H_2</u>), 2.58 (1H, ddd, *J* = 12.0, 5.0, 3.5 Hz, 1 × C**12**-<u>H_2</u>), 1.99 (1H, dddd, *J* = 14.5, 10.0, 4.5, 3.0 Hz, 1 × C**10**-<u>H_2</u>), 1.86 (1H, m, 1 × C**10**-<u>H_2</u>), 1.80 – 1.62 (2H, m, C**11**-<u>H_2</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.3 (C**15**), 136.6 (C**1**), 134.4 (C**8**), 129.4 (C**16**), 128.8 (C**17**), 127.8 (C**18**), 127.5 (**C3**), 121.7 (C**6**), 119.4 (C**5**), 118.1 (C**4**), 111.1, 111.0 (C**2** and C**7**), 67.5 (C**9**), 64.0 (C**14**), 56.9 (C**12**), 51.2 (C**13**), 35.6 (C**10**), 24.0 (C**11**); HRMS: $(ESI)^+$ Calculated for $C_{20}H_{23}N_2O$: 307.1805. Found $[M + H]^+$: 307.1805.

2-Benzyl-6-hydroxy-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-1-one (382) and **2-Benzyl-2,3,4,5,6,7-hexahydro-1H-azocino[4,3-*b*]indol-6-ol (390')** and **2-Benzyl-2,3,4,5,6,7-hexahydro-1H-azocino[4,3-*b*]indole (391)**



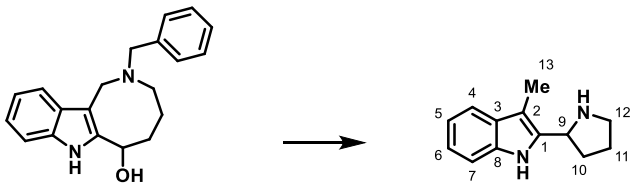
BH3·THF (6.2 mL, 2.00 mmol) was added to a stirring solution of indole **179a** (318 mg, 1.00 mmol) in THF (5 mL) at 0 °C over 10 minutes. The resulting solution was warmed to room temperature and then heated at reflux for 48 hours. The reaction mixture was cooled to 0 °C and quenched by the addition of MeOH (~ 2 mL) until no more effervescence was observed and stirred for 15 minutes. The quenched reaction was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (20–40% EtOAc/hexane) to give the title compound **390'** (50.5 mg, 10%) as colourless oil, the title compound **391** (89.9 mg, 29%) as a colourless oil and the title compound **382** (20.5 mg, 20%) as a white

solid. *The spectroscopic properties of **382** were consistent with the data previously reported in this thesis*.

Data for product **390'**: ν_{max}/ cm^{-1}: 3390 (s), 2928 (w), 2330 (br. s), 2279 (m), 1454 (s), 1163 (s), 1070 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (1H, br. s, NH)), 7.61 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.44 (1H, ddd, *J* = 8.0, 1.0, 1.0 Hz, C**7**-H), 7.38 – 7.13 (7H, m, C**5**-H, C**6**-H, 2 × C**16**-H, 2 × C**17**-H and C**18**-H), 5.11 (1H, dd, *J* = 10.5, 3.5 Hz, C**9**-H), 4.32 (2H, s, C**13**-H_2), 4.18 (1H, d, *J* = 11.5 Hz, 1 × C**14**-H_2), 3.82 (1H, d, *J* = 11.5 Hz, 1 × C**14**-H_2), 2.74 (1H, ddd, *J* = 12.5, 9.5, 1.5 Hz, 1 × C**12**-H_2), 2.49 – 2.17 (3H, m, 1 × C**10**-H_2, 1 × C**11**-H_2 and 1 × C**12**-H_2), 1.94 – 1.76 (2H, m, 1 × C**10**-H_2 and 1 × C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.6 (C**1**), 134.7 (C**8**), 133.4 (C**16**), 132.1 (C**15**), 129.5 (C**3**), 128.6 (C**18**), 127.6 (C**17**), 122.2 (C**6**), 120.9 (C**4**), 118.4 (C**5**), 111.6 (C**7**), 100.7 (C**2**), 68.4 (C**9**), 66.8 (C**14**), 55.2 (C**12**), 54.6 (C**13**), 37.5 (C**10**), 19.2 (C**11**); HRMS: (ESI^+) *Mass peak of the borane adduct **390'***; Calculated for $C_{20}H_{25}BN_2NaO$: 343.1956. Found $[M + Na]^+$: 343.1921; *Mass peak of the tertiary amine*; Calculated for $C_{20}H_{23}N_2O$: 307.1805. Found $[M + H]^+$: 307.1796.

Data for product **391**: ν_{max}/ cm^{-1}: 3350 (s), 2928 (w), 2334 (br. s), 2277 (m), 1453 (s), 1163 (s), 1017 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (1H, br. s, NH), 7.62 (1H, m, d, *J* = 8.5 Hz, C**4**-H), 7.42 – 7.35 (3H, m, C**7**-H and 2 × C**16**-H), 7.31 – 7.24 (3H, m, 2 × C**17**-H and C**18**-H), 7.22 – 7.14 (2H, m, C**5**-H and C**6**-H), 4.54 (1H, d, *J* = 15.0 Hz, 1 × C**13**-H_2), 4.28 (1H, d, *J* = 15.0 Hz, 1 × C**13**-H_2), 4.18 (d, *J* = 12.0 Hz, 1 × C**14**-H_2), 3.80 (d, *J* = 12.0 Hz, 1 × C**14**-H_2), 3.02 (1H, ddd, *J* = 16.0, 10.0, 3.0 Hz, 1 × C**9**-H_2), 2.89 (1H, ddd, *J* = 16.0, 8.0, 3.0 Hz, 1 × C**9**-H_2), 2.77 (1H, m, 1 × C**12**-H_2), 2.53 (1H, m, 1 × C**12**-H_2), 2.32 (1H, br. m, 1 × C**11**-H_2), 2.10 (1H, br. m, 1 × C**10**-H_2), 1.86 – 1.67 (2H, m, 1 × C**10**-H_2 and 1 × C**11**-H_2); ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.3 (C**1**), 134.8 (C**8**), 133.3 (C**16**), 132.3 (C**15**), 129.7 (C**3**), 128.5 (C**18**), 127.5 (C**17**), 121.8 (C**6**), 120.6 (C**5**), 118.0 (C**4**), 110.9 (C**7**), 102.9 (C**2**), 66.5 (C**14**), 55.1 (C**13**), 54.8 (C**12**), 27.3 (C**9**), 26.7 (C**10**), 23.5 (C**11**); HRMS: (ESI^+) *Mass peak of the borane adduct **391***; Calculated for $C_{20}H_{25}BN_2Na$: 322.2595. Found $[M + Na]^+$: 322.2552; *Mass peak of the tertiary amine*; Calculated for $C_{20}H_{23}N_2$: 291.1856. Found $[M + H]^+$: 291.1862.

4-Amino-1-(3-methyl-1*H*-indol-2-yl)butan-1-ol (398)

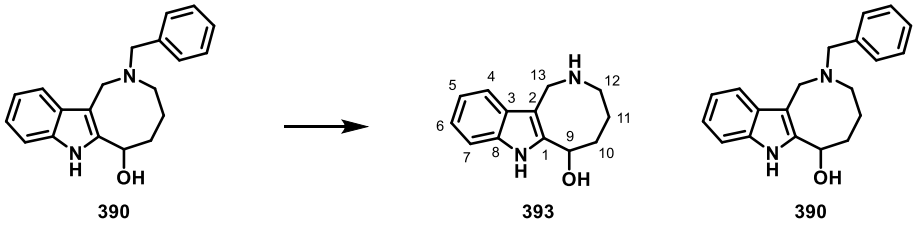


390 **398**

A flame-dried reaction tube, fitted with a magnetic stirrer, was charged with indole **390** (57.5 mg, 0.188 mmol) and ethanol (3.7 mL). The tube was fitted with a rubber septum and purged with argon. Under an atmosphere of argon, 10 wt.% Pd/C (28.8 mg, 0.271 mmol, 50 mol%) was added and the reaction

tube was fitted with a balloon of hydrogen The reaction mixture was sparged with hydrogen gas for 30 seconds, heated to 45 °C under an atmosphere of hydrogen and stirred vigorously for 23 hours. The reaction mixture was cooled to room temperature, degassed with argon and filtered through a pad of celite®, washing with EtOAc (5 mL). The filtrate was concentrated *in vacuo* to afford the title compound **398** (34.6 mg, 92%) as a colourless oil. The product was obtained with good purity and was not purified further. ν_{max}/ cm^{-1}: 3351 (br. s), 2925 (w), 2925 (w), 1460 (m) 1119 (s); ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.43 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.30 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.09 – 6.93 (2H, m, C**5**-H and C**6**-H), 4.99 (1H, t, *J* = 7.0 Hz, C**9**-H), 2.87 – 2.73 (2H, m, C**12**-H_2), 2.29 (3H, s, C**13**-H_3), 2.04 – 1.84 (2H, m, C**10**-H_2), 1.77 – 1.46 (2H, m, C**11**-H_2); ^{13}C NMR (101 MHz, Methanol-d_4): δ 137.2 (2 signals, C**1** and C**8**) 130.2 (C**3**), 122.3 (C**6**), 119.4 (C**5**), 119.1 (C**4**), 111.8 (C**7**), 107.6 (C**2**), 67.0 (C**9**), 41.3 (C**12**), 35.2 (C**10**), 26.8 (C**11**), 8.6 (C**13**); HRMS: $(ESI)^+$ Calculated for $C_{13}H_{17}N_2$: 201.1403. Found $[M + H]^+$: 201.1406.

2,3,4,5,6,7-Hexahydro-1*H*-azocino[4,3-*b*]indol-6-ol (393)

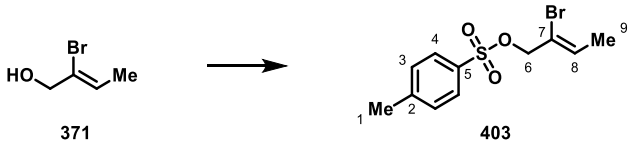


This procedure was carried out in 4 identical reaction tubes in parallel. A flame-dried reaction tube, fitted with a magnetic stirrer, was charged with 20 wt.% $Pd(OH)_2$ (11.5 mg, 0.0821 mmol, 20 mol%). The tube was fitted with a rubber septum and purged with argon. Indole **390** (57.5 mg, 0.188 mmol) was added as a solution in ethanol (3.75 mL). The reaction mixture was sparged with hydrogen gas for 30 seconds and then stirred vigorously under an atmosphere of hydrogen at room temperature for 13 hours. The reaction mixture was degassed with argon and *at this point, the 4 identical reaction tubes were combined* and filtered through a pad of celite®, washing with EtOAc (25 mL). The filtrate was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (10–15% MeOH/CH_2Cl_2 modified with 1% Et_3N) to afford the title compound **393** (92.6 mg, 57%) as a colourless oil and recovered starting material **390** (85.1 mg, 37%) as a colourless solid. *The spectroscopic properties of recovered starting material **390** were consistent with the data previously reported in this thesis.*

Data for major product **393**: ν_{max}/ cm^{-1}: 3252 (br. s), 2926 (m), 1456 (s), 1341 (m), 1021 (s); ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.54 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.37 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.15 – 7.02 (2H, m, C**5**-H and C**6**-H), 5.12 (1H, dd, *J* = 6.5, 3.5 Hz, C**9**-H), 4.67 (1H, d, *J* = 14.5 Hz, 1 × C**13**-H_2), 4.32 (1H, d, *J* = 14.5 Hz, 1 × C**13**-H_2), 2.91 (2H, dt, *J* = 5.5, 3.0 Hz, C**12**-H_2), 2.16 – 1.80 (4H, m, C**10**-H_2 and C**11**-H_2); ^{13}C NMR (126 MHz, Methanol-d_4): δ 140.9 (C**1**), 135.4 (C**8**), 127.3 (C**3**), 121.6 (C**6**),

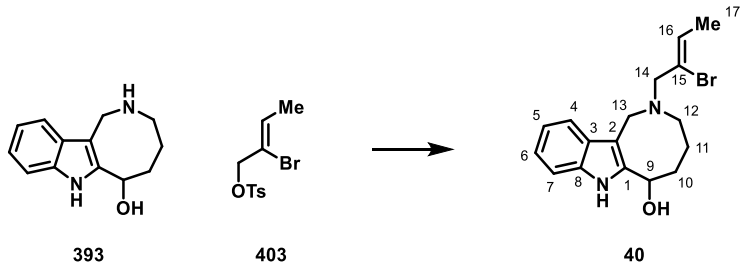
119.5 (C**5**), 117.1 (C**4**), 111.1 (C**7**), 99.9 (C**2**), 66.3 (C**9**), 43.2 (C**12**), 38.2 (C**13**), 35.4 (C**10**), 19.5 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{13}H_{17}N_2O$: 217.1335. Found [M + H]$^+$: 217.1337.

(*Z*)-2-Bromobut-2-en-1-yl 4-methylbenzenesulfonate (403



To a solution of alcohol **371** (146 g, 9.80 mmol), Et_3N (1.59 mL, 10.8 mmol) and DMAP (127 mg, 10 mol%) in CH_2Cl_2 (30 mL) was added tosyl chloride (1.86 g, 9.80 mmol) and the reaction mixture was stirred at room temperature for 18 hours. H_2O (50 mL) was added and the solution was extracted with CH_2Cl_2 (2 × 30 mL). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10 % EtOAc/hexane) to afford the title compound **403** (659 mg, 44%) as a colourless oil; ν_{max}/ cm^{-1}: 2945 (w), 1659 (w), 1598 (w), 1359 (s), 1189 (s), 1176 (s), 940 (s), 813 (s) 667 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.75 (2H, m, 2 × C**4**-H), 7.41 – 7.29 (2H, m, 2 × C**3**-H), 6.13 (1H, qt, *J* = 6.5, 1.0 Hz, C**8**-H), 4.68 (2H, qd, *J* = 1.0, 1.0 Hz, C**6**-H_2), 2.45 (3H, s, C**1**-H_3), 1.71 (3H, dt, *J* = 6.5, 1.0 Hz, C**9**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.1 (C**2**), 133.4 (C**5**), 131.4 (C**8**), 129.9 (C**3**), 128.2 (C**4**), 119.2 (C**7**), 74.5 (C**6**), 21.8 (C**1**), 16.8 (C**9**); HRMS: (ESI)$^+$ Calculated for $C_{11}H_{13}{}^{79}BrN_2O_3S$: 326.9661. Found [M + H]$^+$: 326.9656.

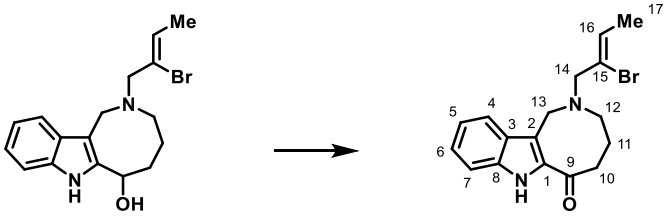
(*Z*)-2-(2-Bromobut-2-en-1-yl)-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-6-ol (401)



To a suspension of amine **393** (76.0 mg, 0.351 mmol), K_2CO_3 (49.7 mg, 0.369 mmol) in DMF (2 mL) was added tosylate **403** (112 mg, 0.369 mmol). The reaction mixture was stirred at room temperature for 18 hours and then CH_2Cl_2 (15 mL) was added. The solution was washed with water (2 × 30 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (50–70% EtOAc/hexane) to afford the title compound **401** (87.9 mg, 72%) as a white solid; m.p.: 71 –72 °C (MeOH); ν_{max} / cm^{-1}: 3397 (w), 3222 (w), 2919 (w), 1457 (m), 1340 (m), 1233 (m), 908 (s), 734 (s), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (1H, br. s, NH), 7.38 (1H, dd *J* = 8.0, 1.0 Hz, C**4**-H), 7.27 (dd, *J* = 8.0, 1.0 Hz, C**7**-H), 7.17 – 7.05 (2H, m, C**5**-H and C**6**-H), 6.04 (1H, q, *J* = 6.5 Hz, C**16**-H), 4.96 (1H, br. m, C**9**-H), 4.10 (d, *J* = 15.5, Hz, 1 × C**13**-H_2), 3.66 (d, *J* = 15.5, Hz, 1 × C**13**-H_2),

3.59 – 3.47 (2H, m, C**14**-H$_2$), 2.84 (1H, m, 1 × C**12**-H$_2$), 2.55 (1H, m, 1 × C**12**-H$_2$), 2.05 (1H, m, 1 × C**10**-H$_2$), 1.88 (1H, m, 1 × C**10**-H$_2$), 1.80 – 1.69 (5H, m, C**11**-H$_2$ and C**17**-H$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.6 (C**1**), 134.4 (C**8**), 128.3 (C**16**), 127.6 (C**3**), 125.0 (C**15**), 121.7 (C**6**), 119.4 (C**5**), 118.0 (C**4**), 111.1 (C**7**), 110.6 (C**2**), 68.5 (C**14**), 67.5 (C**9**), 56.7 (C**12**), 50.9 (C**13**), 35.7 (C**10**), 24.1 (C**11**), 17.0 (C**17**); HRMS: (ESI)$^+$ Calculated for $C_{17}H_{22}{}^{79}BrN_2O$: 349.0910. Found [M + H] $^+$: 349.0904.

(*Z*)-2-(2-Bromobut-2-en-1-yl)-1,2,3,4,5,7-hexahydro-6*H*-azocino[4,3-*b*]indol-6-one (367)



Compound **367** was prepared *via* two alternative methods: ***Method A*** or ***Method B***

Method A: To a solution of alcohol **401** (10.0 mg, 0.290 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (15.3 mg, 0.0319 mmol). The resulting solution was stirred for 4 hours at room temperature. The reaction mixture was diluted with CH_2Cl_2 (5 mL), quenched by the addition of 5% aqueous $Na_2S_2O_3$ solution (2 mL) and saturated aqueous $NaHCO_3$ (2mL) and stirred until all the solids dissolved. The organic layer was separated and washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20–30% EtOAc/hexane) to afford the title compound **367** (7.22 mg, 72%) as a colourless solid.

***Method B*:** To a solution of alcohol **401** (50.0 mg, 0.143 mmol) in acetone (2 mL) was added activated MnO_2 (370 mg, 5.03 mmol, 30.0 equiv.) and the resulting black suspension was stirred at room temperature for 16 hours. The reaction mixture was filtered through Celite®, washing with EtOAc (10 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (0–20% Et_2O/toluene) to yield the title compound **367** (30.3 mg, 61%) as a colourless solid.

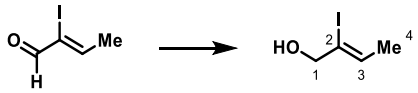
Data for compound **367**: m.p.: 112–114 °C (MeOH); ν_{max} / cm^{-1}: 3315 (br. m), 2920 (w), 1637 (s), 1525 (m), 1443 (m), 1335 (s), 744 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (1H, s, NH), 7.67 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.46 – 7.31 (2H, m, C**6**-H and C**7**-H), 7.17 (1H, ddd, *J* = 8.0, 6.5, 1.0 Hz, C**5**-H), 5.92 (1H, q, *J* = 6.5 Hz, C**16**-H), 4.41 (2H, s, C**13**-H$_2$), 3.29 (2H, s, C**14**-H$_2$), 3.07 (2H, t, *J* = 7.0 Hz, C**10**-H$_2$), 2.69 – 2.61 (2H, m, C**12**-H$_2$), 2.05 (2H, tt, *J* = 7.0, 7.0 Hz, C**11**-H$_2$), 1.78 (3H, d, *J* = 6.5 Hz, C**17**-H$_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.7 (C**9**), 136.0 (C**8**), 134.5 (C**1**), 128.4 (C**3**), 126.5 (2 signals, C**6** and C**16**), 121.0 (C**4**), 120.7 (C**5**), 116.2 (C**2**), 112.0 (C**7**), 110.1 (C**15**), 65.0 (C**14**), 50.0 (C**12**), 47.1

(C**13**), 40.2 (C**10**), 23.6 (C**11**), 16.7 (C**17**); HRMS: (ESI)$^+$ Calculated for $C_{17}H_{20}{}^{79}BrN_2O$: 347.0754. Found [M + H]$^+$: 347.0751.

(*Z*)-2-iodobut-2-enal

To a solution of *trans*-crotonaldehyde (4.14 mL, 50.0 mmol) in 1:1 THF/H_20 (300 mL) at 0 °C was added K_2CO_3 (8.28 g, 60.0 mmol), iodine (19.0 g, 75.0 mmol) and DMAP (1.22 g, 10.0 mmol). The reaction mixture was stirred at 0 °C for 1 hour and then warmed to room temperature and stirred for an additional 1.5 hours. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (40 mL). The aqueous layer was extracted with Et_2O (2 × 75 mL). The organic layers were combined, washed with 0.1 M aq. HCl (30 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound (*Z*)-2-iodobut-2-enal (7.81 g, 80%, >95:5 *Z*:*E*) as an orange oil. The product was used in the following step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (1H, d, *J* = 1.0 Hz, C**1**-H), 7.26 (1H, qd, *J* = 6.5, 1.0 Hz, C**3**-H), 2.17 (3H, d, *J* = 6.5 Hz, C**4**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 186.2 (C**1**), 151.3 (C**3**), 113.2 (C**2**), 18.1 (C**4**). *The spectroscopic properties of this compound were consistent with the data available in literature*.[251]

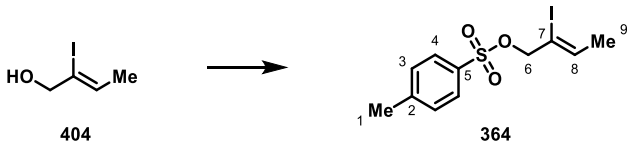
(*Z*)-2-Iodobut-2-en-1-ol (404)



404

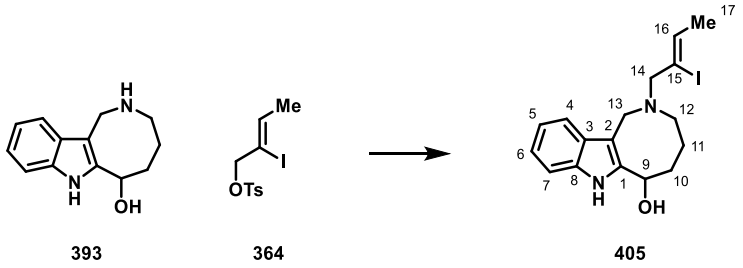
To a solution of (*Z*)-2-iodobut-2-enal (7.81 g, 40.1 mmol) in MeOH (130 mL) at 0 °C was added $NaBH_4$ (2.27 g, 60.1 mmol) portion wise over 10 minutes. The reaction was warmed to room temperature, stirred for 2 hours and then concentrated *in vacuo*. Saturated aqueous $NaHCO_3$ (100 mL) and CH_2Cl_2 (50 mL) were added, the layers were separated and the aqueous portion was further extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (20–50% EtOAc/hexane) to give the title compound (1.69 g, 21%) as a pale yellow oil. ^{1}H NMR (400 MHz $CDCl_3$): δ 5.95 (1H, qt, *J* = 6.5, 1.5 Hz, C**3**-H), 4.28 – 4.16 (2H, d, *J* = 6.5 Hz, C**1**-H_2), 2.22 (1H, m, OH), 1.77 (3H, dt, *J* = 6.5, 1.5 Hz, C**4**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 131.5 (C**3**), 109.8 (C**2**), 71.7 (C**1**), 21.5 (C**4**). *The spectroscopic properties of this compound were consistent with the data available in literature*.[251]

(*Z*)-2-Iodobut-2-en-1-yl 4-methylbenzenesulfonate (364)



To a solution of alcohol **404** (500 mg, 2.62 mmol), Et_3N (0.40 mL, 2.88 mmol) and DMAP (32.0 mg, 10 mol%) in CH_2Cl_2 (6 mL) was added tosyl chloride (497 mg, 2.62 mmol) and the reaction mixture was stirred at room temperature for 18 hours. H_2O (15 mL) was added and the solution was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (0–20% Et_2O/hexane) to afford the title compound **364** (400 mg, 43%) as a pale yellow oil; ν_{max} / cm^{-1}: 2922 (w), 1597 (w), 1355 (s), 1172 (s), 929 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.72 (2H, m, 2 × C**4**-H), 7.46 – 7.30 (2H, m, 2 × C**3**-H), 6.02 (1H, qt, *J* = 6.5, 1.0 Hz, C**8**-H), 4.71 (2H, dt, *J* = 1.0, 1.0 Hz, C**6**-H_2), 2.44 (3H, s, C**1**-H_3), 1.71 (3H, dt, *J* = 6.5, 1.0 Hz, C**9**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.1 (C**2**), 137.5 (C**8**), 133.3 (C**5**), 129.9 (C**3**), 128.2 (C**4**), 98.0 (C**7**), 77.5 (C**5**), 21.8, 21.71 (C**1** and C**9**); LRMS: $(ESI)^+$ Calculated for $C_{11}H_{13}NaIO_3S$: 374.96. Found $[M + Na]^+$: 375.00. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[324]

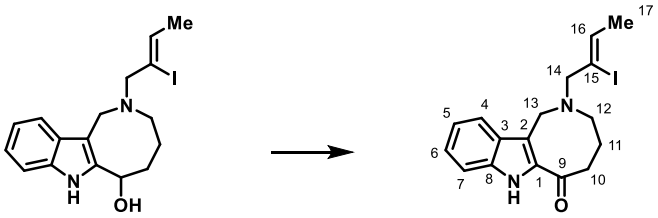
(*Z*)-2-(2-Iodobut-2-en-1-yl)-2,3,4,5,6,7-hexahydro-1*H*-azocino[4,3-*b*]indol-6-ol (405)



To a solution of amine **393** (81.3 mg, 0.376 mmol), K_2CO_3 (53.5 mg, 0.387 mmol) in DMF (2 mL) was added tosylate **364** (132 mg, 0.376 mmol). The reaction mixture was stirred at room temperature for 18 hours and then CH_2Cl_2 (15 mL) was added. The solution was washed with H_2O (2 × 20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (50–70% EtOAc/hexane) to afford the title compound **405** (76.2 mg, 52%) as a white solid; m.p.: 74–76 °C (MeOH); ν_{max} / cm^{-1}: 3389 (s), 3287 (br. s), 2926 (w), 1457 (s), 1442 (s), 1047 (s), 907 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (1H, s, NH), 7.37 (1H, m, C**4**-H), 7.24 (1H, m, C**7**-H), 7.13 – 7.04 (2H, m, C**5**-H and C**6**-H), 5.92 (1H, m, C**16**-H), 5.06 (1H, t, *J* = 4.5 Hz, C**9**-H), 4.06 (1H, d, *J* = 15.5 Hz, 1 × C**13**-H_2), 3.65 (1H, d, *J* = 15.5 Hz, 1 × C**13**-H_2), 3.62 – 3.48 (2H, m, C**14**-H_2), 2.78 (1H, m, 1 × C**12**-H_2), 2.54 (1H, dt, *J* = 12.0, 5.0 Hz, 1 × C**12**-H_2), 2.03 – 1.82 (2H, m, C**10**-H_2), 1.78 – 1.65 (5H, m, C**11**-H_2 and C**17**-H_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.7 (C**1**), 134.5, 134.4 (C**8** and C**16**), 127.5 (C**3**), 121.5 (C**6**), 119.2 (C**5**), 117.9 (C**4**), 111.2 (C**7**), 110.2 (C**2**), 105.9 (C**15**), 71.9 (C**14**),

67.4 (C**9**), 56.7 (C**12**), 50.9 (C**13**), 35.7 (C**10**), 24.0 (C**11**), 22.1 (C**17**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{22}IN_2O$: 397.0771. Found $[M + H]^+$: 397.0763.

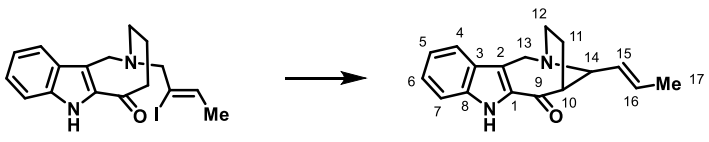
(*Z*)-2-(2-Iodobut-2-en-1-yl)-1,2,3,4,5,7-hexahydro-6*H*-azocino[4,3-*b*]indol-6-one (406)



405 406

To a solution of alcohol **405** (72.0 mg, 0.189 mmol) in acetone (1.9 mL) was added activated MnO_2 (406 mg, 4.73 mmol, 25.0 equiv.) and the resulting black suspension was stirred at room temperature for 16 hours. The reaction mixture was filtered through celite® and concentrated *in vacuo*. The residue was purified by flash column chromatography (0–10% Et_2O/CH_2Cl_2) to yield the title compound **406** (40.3 mg, 54%) as a colourless solid; m.p.: 121–122°C (MeOH); ν_{max} / cm^{-1}: 3313 (br. s), 2921 (w), 1634 (s), 1524 (s), 1442 (s), 1334 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 9.23 (1H, s, N<u>H</u>), 7.65 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-<u>H</u>), 7.44 – 7.30 (2H, m, C**6**-<u>H</u> and C**7**-<u>H</u>), 7.15 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz, C**5**-<u>H</u>), 5.80 (1H, m, C**16**-<u>H</u>), 4.37 (2H, s, C**13**-<u>H_2</u>), 3.25 (2H, br. m, C**14**-<u>H_2</u>), 3.07 (2H, t, *J* = 7.0 Hz, C**10**-<u>H_2</u>), 2.63 (2H, dd, *J* = 7.5, 4.0 Hz, C**12**-<u>H_2</u>), 2.07 – 2.00 (2H, m, C**11**-<u>H_2</u>), 1.79 (3H, dd, *J* = 6.5, 1.5 Hz, C**17**-<u>H_3</u>); ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.9 (C**9**), 136.12 (C**8**), 134.6 (C**1**), 132.3 (C**16**), 128.5 (C**3**), 126.6 (C**6**), 121.1 (C**4**), 120.7 (C**5**), 116.7 (C**2**), 112.2 (C**7**), 110.0 (C**15**), 67.8 (C**14**), 50.0 (C**12**), 47.1 (C**13**), 40.3 (C**10**), 23.7 (C**11**), 21.9 (C**17**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{20}IN_2O$: 395.0615. Found $[M + H]^+$: 395.0616.

(*E*)-12-(prop-1-en-1-yl)-1,4,5,7-tetrahydro-2,5-methanoazocino[4,3-*b*]indol-6(3H)-one (407)

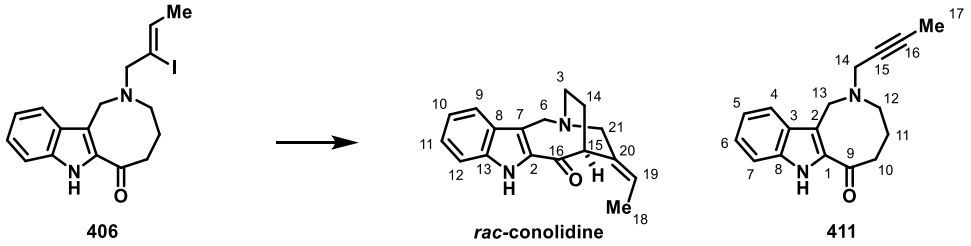


406 407

An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with indole **406** (15.0 mg, 0.038 mmol), Pd_2dba_3 (1.7 mg, 1.9 μmol, 5 mol%), DPEPhos (1.4 mg, 2.6 μmol, 7 mol%) and NaO*t*-Bu (5.5 mg, 0.057 mmol). The tube was fitted with a rubber septum and evacuated and back-filled with N_2 three times. Anhydrous THF (1.0 mL) was added by syringe and the reaction mixture was heated at 80 °C for 18 hours. After this time, the reaction mixture was cooled to room temperature and filtered through celite® and concentrated *in vacuo.* The crude residue was dissolved in 0.5 mL of DMSO and purified by preparative high-performance liquid chromatography using an XSelect CSH C18 OBD Prep column (19 mm x 150 mm, 5 μm). The preprative HPLC was conducted using a 20 mL/min flow rate using a

gradient elution (5–50%, MeCN/H_2O, modified with 0.1% HCl) over 30.0 minutes. The fractions containing the product were concentrated under reduced pressure to give the title compound **407** (1.0 mg, 10%) as an off-white solid. The product **407** was obtained as its HCl salt. *The relative stereochemistry of **407** was not determined.* ν_{max} / cm^{-1}: 3245 (br. m), 2926 (m), 2490 (br. m), 1666 (s), 1456 (m), 1333 (m), 1198 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.87 (1H, br. s), 9.13 (1H, br. s, NH), 7.61 (1H, d, *J* = 8.0 Hz, ArC-H), 7.54 – 7.46 (2H, m, 2 × ArC-H), 7.30 (1H, m, ArC-H), 6.37 (1H, dd, *J* = 13.5, 6.5 Hz, C**16**-H), 5.55 (1H, d, *J* = 15.5 Hz, C**15**-H), 4.85 – 4.72 (3H, m, C**13**-H_2 and C**14**-H), 4.19 (1H, br. m, 1 × C**12**-H_2), 3.56 (1H, br. m, C**10**-H), 3.45 (1H, br. m, 1 × C**12**-H_2), 2.69 (1H, m, 1 × C**11**-H_2), 2.34 (1H, m, 1 × C**11**-H_2), 1.74 (3H, d, *J* = 5.5 Hz, C**17**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.8 (C**9**), 142.2 (C**16**), 136.9 (ArC), 130.4 (ArC), 128.3 (C**6**), 126.1 (ArC), 122.4 (C**5**), 120.7 (C**4**), 117.7 (C**15**), 112.6 (C**7**), 112.2 (C**2**), 66.7 (C**14**), 53.5 (C**10**), 51.5 (C**12**), 48.2 (C**13**), 29.9 (C**11**), 18.4 (C**17**); HRMS: $(ESI)^+$ Calculated for $C_{17}H_{19}N_2O$: 267.1492. Found $[M + H]^+$: 267.1504. *Due to the small quantity of indole **407**, no further data could be obtained.*

2-(But-2-yn-1-yl)-1,2,3,4,5,7-hexahydro-6*H*-azocino[4,3-*b*]indol-6-one (411) and **preliminary data for (*rac*)-conolidine.**



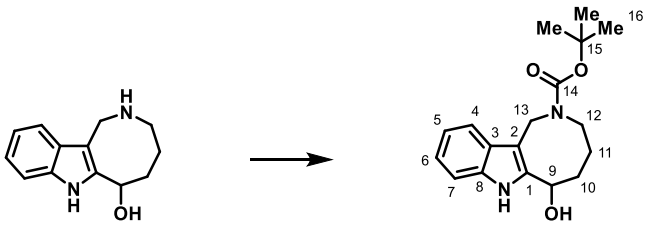
An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with indole **406** (20.0 mg, 0.051 mmol). The tube was fitted with a rubber septum and evacuated and back-filled with N_2 three times. Anhydrous THF (2.0 mL) was added by syringe and the reaction mixture was cooled to 0 °C. LiHMDS (0.10 mL, 0.102 mmol, 1.0 M in THF) was added and the resulting solution was stirred for 1 hour. $NiCl_2(PCy_3)_2$ (10.6 mg, 0.015 mmol) was added and the reaction mixture was stirred for a further 10 minutes at 0 °C. After this time, the reaction tube was sealed and heated at 50 °C for 18 hours. After this time, the reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl (0.5 mL) was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 2 mL). The organic layers were combined, washed with brine (1 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. ^{1}H NMR and ^{13}C NMR analysis of the crude product indicated formation of (*rac*)-conolidine. *Due to the small quantity of (rac)-conolidine, this compound was not isolated and the structure was deduced by analysis and comparison of the ^{1}H NMR and ^{13}C NMR spectra of the crude reaction mixture with the data reported in the literature.*[221,237,247] *These assignments are further corroborated by 2D COSY and HSQC data. The assignment and comparison of diagnostic ^{1}H and ^{13}C signals are provided in Table 25 and Table 26.* The crude material was purified by flash column

chromatography (10–25% solvent A in hexane (solvent A was EtOAc/MeOH (3:1))) to afford the title compound **411** (3.51 mg, 26%) as a colourless solid.

(*rac)*-conolidine: *Diagnostic signals only*: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (1H, d, *J* = 8.0 Hz, C**9**-H), 5.47 (1H, d, *J* = 7.0 Hz, C**19**-H), 4.78 (1H, d, *J* = 18.5 Hz, 1 × C**6**-H_2), 4.27 (1H, d, *J* = 18.5 Hz, 1 × C**6**-H_2), 3.97 (1H, d, *J* = 7.0 Hz, C**15**-H), 3.86 (1H, d, *J* = 16.0 Hz, 1 × C**21**-H_2), 3.41 (1H, m, 1 × C**3**-H_2), 3.32 (1H, d, *J* = 16.0 Hz, 1 × C**21**-H_2), 1.50 (3H, dd, *J* = 7.0, 2.0 Hz, C**18**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.9 (C**16**), 136.3 (C**13**), 133.5 (C**2**), 130.3 (C**20**), 127.9 (C**8**), 126.6 (C**11**), 120.9 (C**9**), 120.6 (C**10**), 120.3 (C**7**), 111.9 (C**12**), 55.1 (C**21**), 53.3 (C**6**), 48.1 (C**15**), 44.2 (C**3**), 22.9 (C**14**), 12.8 (C**18**).

Data for compound **411**: m.p.: 160–162 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (1H, s, NH), 7.84 (1H, dd, *J* = 8.0, 1.0 Hz, C**4**-H), 7.46 – 7.33 (2H, m, C**6**-H and C**7**-H), 7.19 (1H, ddd, *J* = 8.0, 6.5, 1.0 Hz, C**5**-H), 4.58 (2H, s, C**13**-H_2), 3.16 – 3.13 (2H, br. m, C**14**-H_2), 3.08 (2H, t, *J* = 7.5 Hz, C**10**-H_2), 2.65 (2H, t, *J* = 6.0 Hz, C**12**-H_2), 2.13 (2H, tt, *J* = 7.5, 6.0 Hz, C**11**-H_2), 1.85 (3H, t, *J* = 2.5 Hz, C**17**-H_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.1 (C**9**), 136.0 (C**8**), 134.9 (C**1**), 128.9 (C**3**), 126.6 (C**6**), 121.2 (C**4**), 120.9 (C**5**), 115.2 (C**2**), 111.9 (C**7**), 80.5, 75.3 (C**15** and C**16**), 50.0 (C**12**), 46.0, 45.8 (C**13** and C**14**), 40.0 (C**10**), 23.9 (C**11**), 3.6 (C**17**); HRMS: (ESI)$^{+}$ Calculated for $C_{17}H_{19}N$: 267.1492. Found [M + H]$^{+}$: 267.1490. *The spectroscopic properties of this compound were consistent with the data available in the literature.*[356]

***tert*-Butyl 6-hydroxy-1,3,4,5,6,7-hexahydro-2*H*-azocino[4,3-*b*]indole-2-carboxylate (412)**

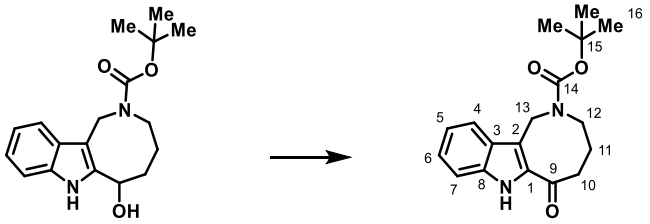


393 **412**

To a solution of amine **393** (20.0 mg, 0.0925 mmol), K_2CO_3 (12.7 mg, 0.0925 mmol) in DMF (1 mL) was added di-*tert*-butyl dicarbonate (20.0 mg, 0.0925 mmol). The reaction mixture was stirred at room temperature for 18 hours and then EtOAc (5 mL) was added. The solution was washed with water (2 × 15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (20–70% EtOAc/hexane) to afford the title compound **412** (12.3 mg, 43%) as a white solid; m.p.: 133–134 °C (MeOH); ν_{max} / cm^{-1}: 3360 (br. s), 2930 (w), 1552 (s), 1417 (s), 1355 (s), 1152 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (1H, s, NH), 7.44 (1H, d, *J* = 8.0 Hz, C**4**-H), 7.32 (1H, d, *J* = 8.0 Hz, C**7**-H), 7.19 – 7.03 (2H, m, C**5**-H and C**6**-H), 5.26 (1H, m, C**9**-H), 5.05 (1H, br. m, 1 × C**13**-H_2), 4.25 (1H, d, *J* = 16.5 Hz, 1 × C**13**-H_2), 3.90 (1H, br. m, 1 × C**12**-H_2), 2.97 (1H, d, *J* = 14.0 Hz, 1 × C**12**-H_2), 2.66 (1H, s, OH), 2.09 (1H, m, 1 × C**10**-H_2), 1.71 (3H, br. m, 1 × C**10**-H_2 and C**11**-

$\underline{H}_2$), 1.44 (9H, s, 3 × C**16**-$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7 (C**14**), 135.5 (C**1**), 134.5 (C**8**), 127.5 (C**3**), 121.4 (C**6**), 119.3 (C**5**), 118.0 (C**4**), 110.9 (C**7**), 107.4 (C**2**), 79.9 (C**15**), 67.2 (C**9**), 46.6 (C**12**), 43.0 (C**13**), 36.9 (C**10**), 28.6 (C**16**), 24.4 (C**11**); HRMS: (ESI)$^+$ Calculated for $C_{18}H_{24}N_2NaO_3$: 339.1679. Found [M + Na]$^+$: 339.1672.

***tert*-Butyl 6-oxo-1,3,4,5,6,7-hexahydro-2*H*-azocino[4,3-*b*]indole-2-carboxylate (362)**



412 **362**

To a solution of alcohol **412** (5.0 mg, 0.0158 mmol) in acetone (0.3 mL), was added activated MnO_2 (41.3 mg, 0.475 mmol, 30.0 equiv.) and the resulting black suspension was stirred at room temperature for 3 hours. The reaction mixture was filtered through celite®, washing with EtOAc (2 mL) and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% EtOAc/hexane) to yield the title compound **362** (4.3 mg, 86%, 1:1 mixture of rotamers *A*:*B*) as a colourless solid; ν_{max} / cm^{-1}: 3320 (br. s), 2973 (w), 1677 (s), 1638 (s), 1453 (m), 1408 (s), 1152 (s), 1550 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.39 – 9.10 (2H, br. m, N$\underline{H}$, *A*+*B*), 7.89 – 7.68 (2H, m, C**4**-$\underline{H}$, *A*+*B*), 7.44 – 7.35 (4H, m, C**6**-$\underline{H}$ and C**7**-$\underline{H}$, *A*+*B*), 7.23 – 7.15 (2H, m, C**5**-$\underline{H}$, *A*+*B*), 5.03 (2H, s, C**13**-$\underline{H}_2$, *A*), 4.90 (2H, s, C**13**-$\underline{H}_2$, *B*), 3.72 – 3.59 (2H, br. m, C**12**-$\underline{H}_2$, *A*), 3.57 – 3.43 (2H, br. m, C**12**-$\underline{H}_2$, *B*), 3.04 – 2.92 (4H, m, C**10**-$\underline{H}_2$, *A*+*B*), 2.12 – 1.92 (4H, m, C**11**-$\underline{H}_2$, *A*+*B*), 1.52 (9H, s, 3 × C**16**-$\underline{H}_3$, *A*), 1.33 (9H, s, 3 × C**16**-$\underline{H}_3$, *B*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.4, 192.7 (C**9**, *A*+*B*), 155.4, 155.3 (C**14**, *A*+*B)*, 135.9, 135.7 (C**8**, *A*+*B*), 133.9, 132.7 (C**1**, *A*+*B*), 128.1, 127.7 (C**3**, *A*+*B*), 126.9, 126.7 (C**6**, *A*+*B*), 121.1 (2 signals, C**4**, *A*+*B*), 120.9, 120.5 (C**5**, *A*+*B*), 119.5, 117.5 (C**2**, *A*+*B*), 112.0 (C**7**, *A*+*B*), 80.2, 80.1 (C**15**, *A*+*B*), 46.4 (C**12**, *A*), 43.3 (C**12**, *B*), 42.7, 42.6 (C**13**, *A*+*B*), 39.5, 38.7 (C**10**, *A*+*B*), 28.5, 28.4 (C**16**, *A*+*B*), 25.1, 24.0 (C**11**, *A*+*B*); HRMS: (ESI)$^+$ Calculated for $C_{18}H_{22}N_2NaO_3$: 337.1523. Found [M + Na]$^+$: 337.1532. *The spectroscopic properties of this compound were consistent with the data available in the literature*.[250]

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